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SURGICAL DISEASES

OF THE

THYROID GLAND

BY

E. M. EBERTS, M.D.

SURGEON TO THE MONTREAL GENERAL HOSPITAL; ASSOCIATE PROFESSOR OF SURGERY, McGILL UNIVERSITY

WITH THE ASSISTANCE OF

R. R. FITZGERALD, M.D.

AND

PHILIP G. SILVER, M.D.

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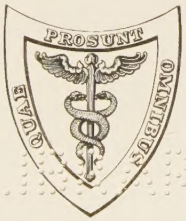

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TO

THE ATTENDING STAFF

OF

THE MONTREAL GENERAL HOSPITAL

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PREFACE.

In preparing this text upon the surgical diseases of the thyroid gland my aim has been to present the subject in a practical way and within reasonable compass.

In the clinical field the views expressed are based upon personal experience in the Goiter Clinic of the Montreal General Hospital, where patients not only receive immediate treatment but are examined periodically for several years after operation. The records of out-of-town patients are kept up to date by questionnaires sent out at intervals to the family physician. In this clinic there have been investigated 2250 cases, of which 1050 have been treated surgically. In order, however, that the results might be checked by follow-up observations of not less than one year, only those cases operated upon prior to 1928 have been included in the statistical tables.

The development of a goiter clinic at the Montreal General Hospital has been possible owing to the encouragement and generous support of the Attending Staff as a whole and the sustained interest and close coöperation of those members of the staff who have participated directly in its work. I am deeply indebted to Dr. C. K. P. Henry for taking charge of the clinic and the operative work during my absence; to Dr. I. M. Rabinowitch for organizing and maintaining a prompt and efficient metabolic service in connection with the clinic; to Dr. C. C. Birchard, Associate

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Physician in charge of the Electrocardiographic Department, for the elucidation of cardiograms; and to Dr. E. B. Chandler, Dr. R. R. Fitzgerald, and Dr. P. G. Silver, attached to my Surgical Division, for faithful service in the out-patient clinic and in the operating room.

For the subject matter of the chapters on Pathology and Malignant Disease contemporaneous opinion has been liberally drawn upon.

The microphotographs illustrating the chapter on Embryology were made by Dr. Fitzgerald in Professor Fischel's laboratory in Vienna and are reproduced in the text with the kind permission of Professor Fischel. I am indebted to Dr. Fitzgerald also for making the microphotographs illustrating the chapters on Histology and Pathology and for assembling the material from which Part I has been written.

To Dr. Silver has fallen the arduous task of compiling the statistics. Over 700 case reports have been exhaustively reviewed and tabulated.

The anatomical drawing and those illustrating operative technique are by Miss Hortense Douglas, Artist to the Hospital.

I am greatly indebted to Dr. H. A. Lafleur and to Dr. Edward Archibald for criticizing the manuscript and suggesting improvements.

E. M. E.

Montreal, Canada.

FOREWORD.

There are but few books in English upon goiter; and of these not all deserve the seal of unqualified approval. Should a man desire to increase his knowledge of the diseases of the thyroid, to find a sure path in an unfamiliar field, he turns to an inchoate mass of journal articles, and in the event is left confused. He needs a leader. So that there is not only room for a book on the subject of the sort that my friend and colleague has written; there is also a real need.

Here one will find set forth in orderly fashion the knowledge acquired not only, or merely, through the management of many cases, but also through a conscientious study of those cases. The number of patients available to the author for study is ideal; not that multitude which creates confusion through very unwieldiness; not that paucity which leads to false conclusions. I am convinced that in no "thyroid clinic" has there been carried out more careful study of histories, more complete laboratory examinations, more persistent following of the patients, or more rigid scanning of the results of treatment. The work bears the hall-mark of personal experience. And to all this there has been added, as I know, a wide knowledge of the work and opinions of others on both sides of the Atlantic.

Dr. Eberts has done well to avoid long discussions concerning the unresolved problems of etiology or of classification or of toxicity. This is not a detail map; it is a guide book,

indicating the best routes and the safest stopping places, written by one who has travelled far and travelled wisely. In this world of shifting sand, if one may apply the metaphor to the confusions of much of the recent literature on thyrotoxicosis, it is a useful thing to possess such a guide book. "No household should be without one." The undergraduate, the general practitioner, the busy practical surgeon, and, perhaps especially, he who is a student of this subject—each and all will find profit in this book, and will find also that pleasure which comes from the perusal of what has been well pondered and is well expressed.

EDWARD ARCHIBALD.

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SURGICAL DISEASES OF THE THYROID GLAND.

PART I.

CHAPTER I.

EMBRYOLOGY OF THE THYROID GLAND.

When the human embryo is 1.5 mm. long, a shallow depression can be seen in the primitive pharynx between the ventral extremities of the first pair of gill pouches (Fig. 1). This is the thyroid pouch—the precursor of the thyroid gland, which is the first parenchymatous organ to appear.

The epithelial cells in the floor of the pouch multiply and grow caudally, forming a mass which gradually descends through the developing muscles of the base of the tongue, in front of the epiglottis and primitive larynx, down to the upper part of the trachea, where it comes to rest. As it descends, it draws the pouch out into a long tube, known as the thyroglossal duct (Fig. 2), the opening to which at the root of the tongue is called the foramen cecum. This duct is normally obliterated during fetal life.

The cells of the embryonic thyroid now multiply and spread laterally. The mass is at first solid, but later open spaces appear. Still later these open spaces become filled with a growing vascular and lymphoid tissue, which ultimately splits the thyroid epithelium into wavy or convoluted plates, usually two cells in thickness (Figs. 3, 4 and 5).

In the meantime the larynx has been developing, and, as

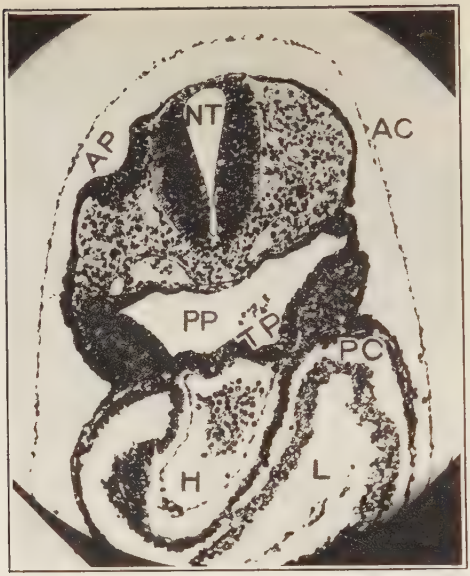

FIG. 1.—Coronal section through the cranial end of a human embryo of four somites. *A.C.*, amnion and chorion; *N.T.*, the neural tube (primitive brain); *A.P.*, auditory plate; *P.P.*, the primitive pharynx; *T.P.*, the thyroid pouch; *H.*, the heart with blood cells; *P.C.*, the pleural cavity; *L.*, the lung.

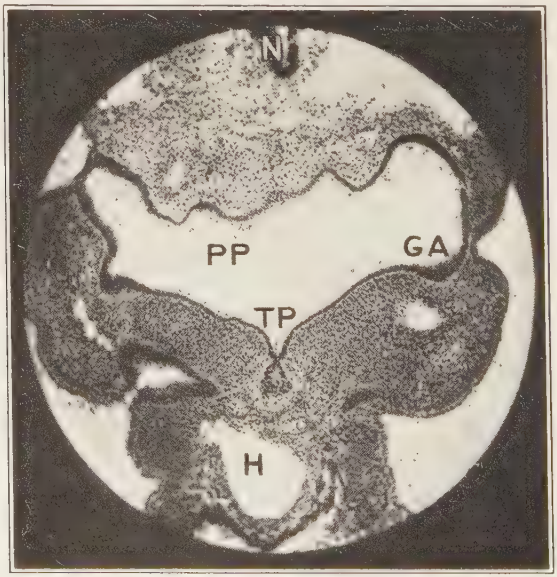

FIG. 2.—Frontal section through the pharynx of an early human embryo. *N.T.*, the neural tube; *P.P.*, the primitive pharynx; *G.A.*, the gill arch; *T.P.*, the thyroid pouch with constricted neck; *H.*, the heart.

the thyroid cartilage grows forward, it divides the thyroid tissue into two lobes connected by an isthmus.

When the embryo is 15 mm. long, the two layers of cells forming the plates become separated at irregular intervals

FIG. 3.—Frontal section, young human embryo. *P.*, pharynx; *F.C.*, foramen cecum; *T.*, tongue; *T.A.*, thyroid body, showing lateral development and ingrowth of lymphoid and vascular elements, dividing the parenchyma into "plates," two cells in thickness. The thyroglossal duct is seen as a vertical column of cells extending downward from foramen cecum.

by a clear substance. This is the origin of the adult vesicle (Figs. 6 and 7). More and more vesicles are formed; foci of lymphoid tissue appear throughout the gland, and a capsule of fibrous connective tissue gradually envelops it.

The most striking features of thyroid embryology are:

FIG. 4.—Horizontal section, young human embryo. *O.*, esophagus; *T.*, trachea; *T.A.*, thyroid body; *U.B.*, ultimo branchial body.

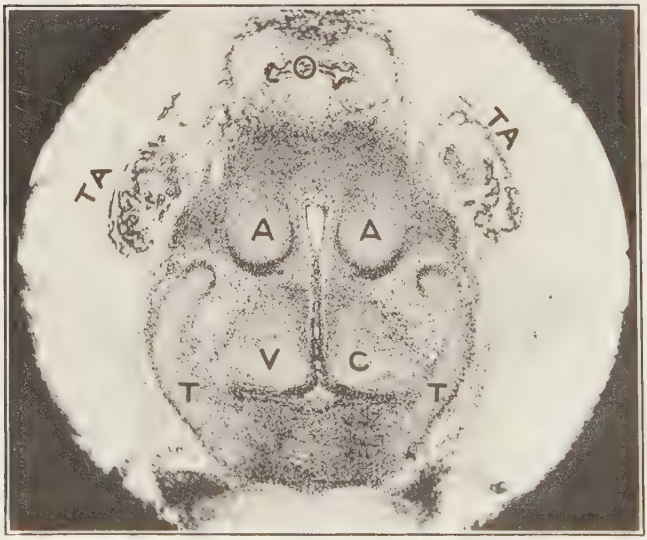

FIG. 5.—Horizontal section through the larynx—young human embryo. *O.*, esophagus; *T.A.*, thyroid body, right and left lobes, in convoluted plate stage; *A.*, arytenoid cartilage; *T.*, thyroid cartilage; *V.C.*, vocal cords.

(1) the early appearance of the primitive thyroid; (2) the distance traversed by the maturing gland; and (3) the development of alveoli at intervals along an already existing plaque of epithelial cells.

FIG. 6.—Human embryo. Transverse section. *V.*, vertebra; *O.*, esophagus; *T.R.*, and *T.L.*, right and left thyroid lobes; *V.C.*, vocal cords; *H.B.*, hyoid bone; *T.*, tongue; *S.G.*, salivary gland.

Developmental anomalies may occur.

1. The thyroid gland may develop at its site of origin at the base of the tongue (lingual thyroid) or in the region of the hyoid bone after partial descent (submental thyroid). Before

removing tumors in either of these areas, therefore, one should make sure that the thyroid gland is present in its normal position.

2. The thyroglossal duct may persist as a fibromuscular cord, which may contain thyroid tissue. When complete, it extends from the foramen cecum to the isthmus of the gland, passing through the root of the tongue; behind, through,

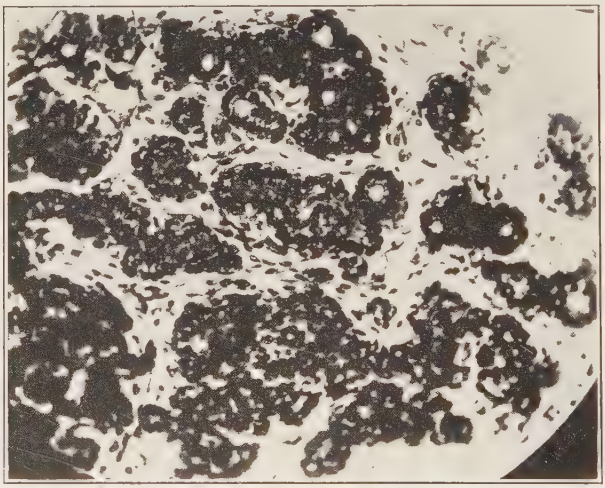

FIG. 7.—Human embryo. High-power photograph of the primitive thyroid. Columns of cells separated by growing fibrous connective tissue. The columns are opening at intervals to form circular spaces filled with clear material (the primitive colloid vesicles).

or in front of the hyoid bone; across the thyrohyoid membrane and in front of the thyroid cartilage. The lumen of the thyroglossal duct may be incompletely obliterated, and cysts may form. Malignant tumors originating in the thyroglossal duct have also been met with. Cases have been observed in which the thyroid secretion was derived entirely from a thyroglossal duct remnant. Before removing a mass in the course of the thyroglossal duct or even interfering

with its blood supply, therefore, one should be satisfied that the thyroid gland is not missing. Otherwise, myxedema may result.

3. Pyramidal lobes may develop at the lower end of the thyroglossal duct. Usually they are single and on the left side. They may, however, be bilateral.

4. The ultimo-branchial body, the mysterious derivative of the fifth branchial pouch which disappears normally during fetal life, may persist. Remnants or derivatives of it are sometimes, though rarely, found in benign or malignant tumors and in inflammatory lesions of the thyroid gland.

5. Accessory thyroid tissue may be present along the course of the thyroglossal duct. Tissue found elsewhere in the neck or in the thorax, however closely it may resemble normal thyroid tissue, is usually neoplastic.

6. One thyroid lobe may be absent. This anomaly is apparently rare, being met with approximately once in every 1000 autopsies.

7. The isthmus may be absent.

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CHAPTER II.

ANATOMY AND HISTOLOGY OF THE THYROID GLAND.

ANATOMY OF THE THYROID GLAND.

The thyroid gland consists of two lobes connected by an isthmus. It lies astride the trachea, to which it is loosely attached. Each lobe covers antero-laterally the lower half of the thyroid cartilage, the cricoid cartilage, and the upper four or six tracheal rings. The ribbon-like isthmus covers the trachea from the second to the fifth ring.

The lobes are convex externally and concave internally. The upper poles are conical; the lower, rounded. The right lobe is generally the larger; it is also higher in the neck than the left and in a slightly anterior plane. These differences in size and position explain: (1) the frequency with which patients suffering from adolescent or exophthalmic goiter assert that, to them, the enlargement has been noticeable in the right lobe alone; (2) the tendency for adenomata in the right lobe to appear above the clavicle, while those in the left lobe (being prevented from growing forward by the upper margin of the sternum, the clavicle, and the lower insertion of the left sternocleidomastoid muscle) are more likely to extend deeply into the neck or down toward the thorax; and (3) the frequency of intrathoracic goiter on the left side as compared with the right (Figs. 47 and 48, pages 189-190).

The mean weight of the thyroid gland (for both sexes), estimated from a study of 231 cases, either taken from the literature or observed personally, is reported by Scammon to be 26.11 gm. (communicated). In collecting weights given by other authors Scammon excluded all cases with a question-

able history and all observations from the "thyroid district" of Europe (Switzerland, South Germany, North Italy and the Tyrol). In 34 cases of young males dying within forty-eight hours after being wounded in battle and autopsied within twelve hours after death, the average weight of the thyroid was found to be 26.6 gm., which conforms closely to the average weight of the 231 cases already quoted. It is Scammon's opinion that the weights usually stated are too high. The average weight of the adult gland in the "Alpine district," as determined from 250 cases in the literature in which thyroid disease could be definitely excluded, was found by Scammon to be 37.66 gm.

The uniformly low gland-weight reported by the Japanese, a race of small people, suggests that there is a definite ratio between gland-weight and body-weight.

There is sometimes a slight physiological increase in the size of the gland at puberty, at menstruation, or during pregnancy.

The blood supply is derived from the superior and inferior thyroid arteries, the inconstant arteria thyroidea ima, and the anastomotic branches of the tracheal, laryngeal and esophageal arteries.

The superior thyroid artery (1.6 mm. in diameter) arises from the external carotid at the level of the upper border of the thyroid cartilage, gives off its sternomastoid branch, and, in close relation with the superior thyroid vein and sympathetic nerve fibers from the middle cervical ganglion, descends to the apex of the upper pole, there breaking up into the posterior, the antero-lateral, and the antero-medial branches. Of these the antero-medial branch is the most constant. It gives off the crico-thyroid artery, which crosses the mid-line at the level of the upper border of the cricoid cartilage to join its fellow from the opposite side. The posterior branch descends to meet the ascending branch of the inferior thyroid artery. The superior vascular stem suspends and fixes the upper pole (Fig. 8).

The inferior thyroid artery (2 mm. in diameter) arises from the thyrocervical axis of the subclavian. It runs a short transverse course toward the mid-line. Resting upon the deep cervical fascia, it passes behind the internal jugular

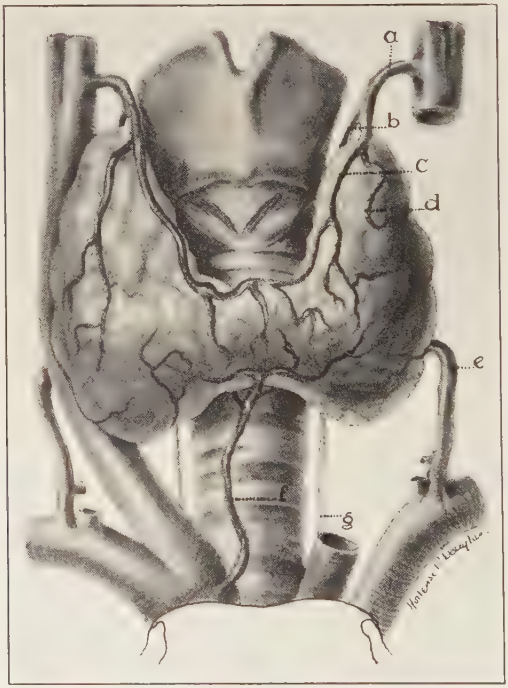

FIG. 8.—Thyroid gland, anterior view, showing arterial supply (semi-diagrammatic). (*a*) Superior thyroid artery; (*b*) posterior branch; (*c*) antero-medial branch; (*d*) antero-lateral branch; (*e*) inferior thyroid artery; (*f*) thyroidea ima artery; (*g*) left recurrent laryngeal nerve.

vein, the vagus nerve, and the carotid artery, reaching the lobe at the junction of its middle and lower third, where it breaks up into several branches. One branch supplies the parathyroid bodies; one, as already stated, anastomoses with the posterior descending branch of the superior thyroid artery;

and the remaining branches enter the gland. Normally the inferior thyroid artery is, throughout its course, widely separated from the sympathetic fibers of the inferior cervical ganglion. Just before it reaches the posterior capsule of the gland, it crosses the recurrent laryngeal nerve—on the right side usually behind the nerve, on the left side more frequently in front of it.

There is an extremely free subcapsular anastomosis between the superior and the inferior thyroid arteries of the same side and also a free anastomosis between the vessels of the two lobes. Fluid injected experimentally into the superior thyroid artery of one side escapes from the inferior thyroid artery of the same side in 100 per cent of cases, from the superior thyroid of the opposite side in 100 per cent, and from the inferior thyroid of the opposite side in 80 per cent. Following injection into the inferior thyroid on one side the fluid escapes from the superior thyroid on the same side in 100 per cent, from the superior thyroid of the opposite side in 80 per cent, and from the inferior thyroid of the opposite side in 20 per cent. This freedom of anastomosis accounts for the evanescent effect of polar ligation.

Within the body of the gland the superior thyroid arteries supply the interstitial tissues; the inferior, the parenchymatous. Anastomoses are few.

The arteria thyroidea ima, when present, arises from the aorta, ascends upon the trachea, and gives off branches to the isthmus and to one or both lobes.

The superior thyroid vein accompanies the superior thyroid artery and drains into the internal jugular vein. The middle thyroid vein accompanies the inferior thyroid artery, and also joins the jugular. As a rule there are several inferior thyroid veins which, arising from the isthmus and lower poles, form a plexus on the anterior surface of the trachea. They empty into the left innominate vein.

The lymphatics of the upper part of the thyroid drain into the deep cervical glands; those from the lower part are

closely connected with the lymphatics of the parathyroids and thymus, and drain into the pretracheal and supraclavicular lymph glands.

The nerve supply is derived from the superior and the recurrent laryngeal branches of the vagus and from the cervical sympathetic ganglia.

The thyroid gland is embraced by the perithyroid fascia, which extends medially from the carotid sheath on each side and is derived from the deep cervical fascia. The perithyroid fascia is attached to the larynx above and blends with the mediastinal tissues below. In front of the thyroid gland are the sternothyroid, sternohyoid and omohyoid muscles, contained in a separate fascial compartment, and at the sides are the sternomastoid muscles, which are also provided with separate fascial sheaths.

The gland is maintained in its normal position by:

1. The suspensory ligament—a dense band of fibrous connective tissue derived from the perithyroid fascia. It extends from the upper border of the thyroid isthmus to the oblique lines on the lateral surfaces of the thyroid cartilages, and is the chief factor in causing the gland to ascend with the larynx on deglutition. The ligament sometimes contains a few muscle fibers.

2. The superior vascular stem. The superior thyroid artery and vein, together with the nerves and lymphatics, form a suspending cord which holds the upper pole of the thyroid in its normal position. The upper pole is in fact the most fixed portion of the lobe and cannot readily be dislodged without division of the vascular stem. Other portions of the gland are, in comparison, freely movable.

3. The close attachment of the sternothyroid muscle to the subjacent surface of the upper pole. If the pole is enlarged, the attachment becomes more intimate.

4. The tonus of the prethyroid group of muscles, which press the gland against the larynx and prevertebral structures.

In contact with the posterior surface of the thyroid and

sometimes embedded in it, are the parathyroid bodies, varying in number from two to seven. Most commonly there are but four, one near the center of each lobe and one behind each lower pole.

HISTOLOGY OF THE THYROID GLAND.

There is a thin capsule of fibrous connective tissue, and from this capsule is derived the stroma which divides the gland into a number of unequal lobules. In this supporting structure are the interlobular bloodvessels, the lymphatics, aggregates of lymphoid cells, and reticulo-endothelial cells.

It is thought that each lobule consists of a convoluted column of epithelial cells, the two layers of which are separated at intervals by colloid material, forming chains of vesicles or acini. Each chain of vesicles is surrounded by a network of blood capillaries, the walls of which consist of a single layer of endothelial cells. When a section of normal thyroid tissue is examined under the microscope, one sees a number of vesicles, closely packed together, lined with cuboidal epithelium, and filled with colloid. There are no partitions between the epithelial cells. The cytoplasm of one cell is believed to be in direct contact with that of the contiguous cells.

Wilson has reconstructed in wax the normal vesicle of the human thyroid and describes it as a discrete, rounded, oval or budded structure, averaging 300 μ in diameter. In his opinion, secondary follicles arise from primary ones by a process of budding or by constriction (Fig. 9).

A recent and interesting theory of gland architecture is that the lobule is a lymph sinusoid in which floats the column of epithelial cells, and that the lymph escapes at the hilus of the lobule into the large interlobular lymphatics.

In the normal gland the epithelium assumes three distinct forms, which are thought to correspond to the two functional

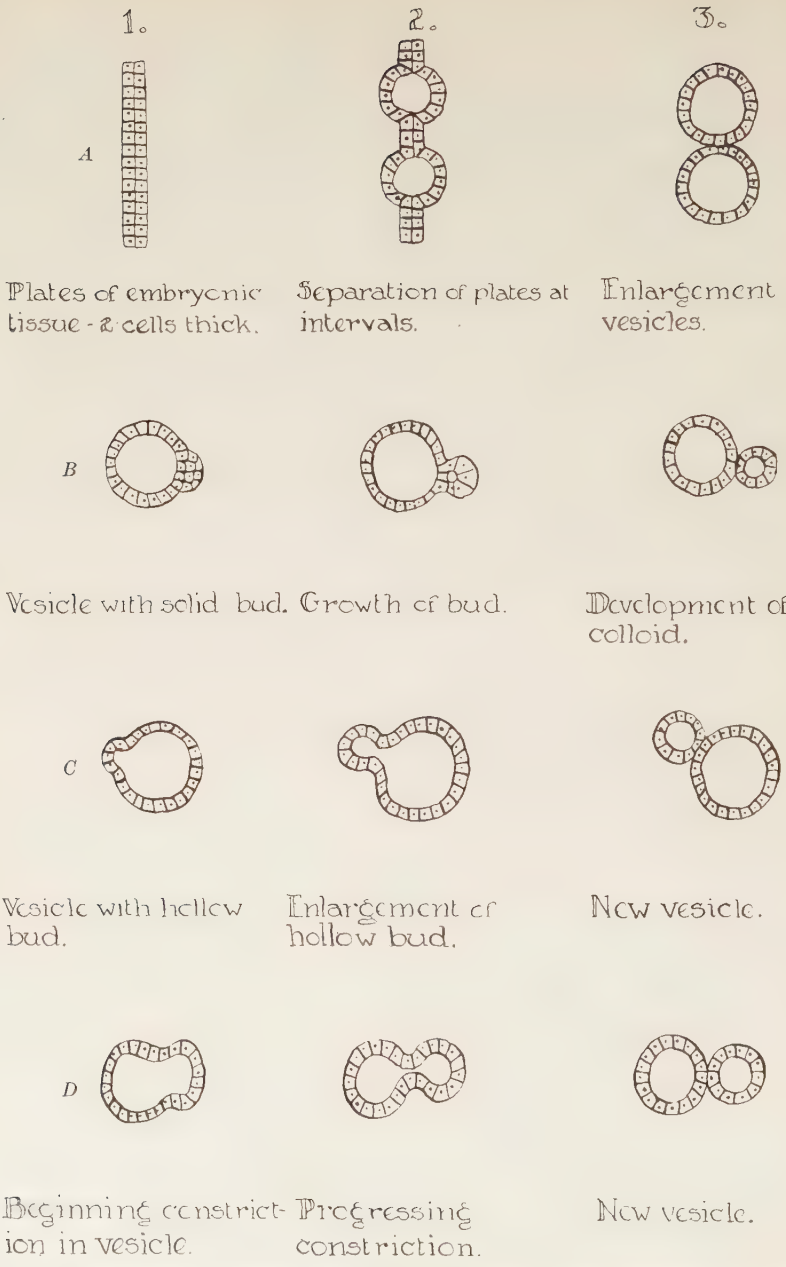

FIG. 9.—Diagrammatic representation of four methods by which vesicles may develop in thyroid tissue. *A*, fetal; *B*, solid buds; *C*, hollow buds; *D*, constriction.

phases and the resting phase described in the chapter on Physiology.

In the colloid storage phase the cells are low-cuboidal or flat in outline, and have a clear-staining cytoplasm and a small, centrally placed, deeply-staining nucleus. The vesicles are completely filled with a homogeneous colloid material.

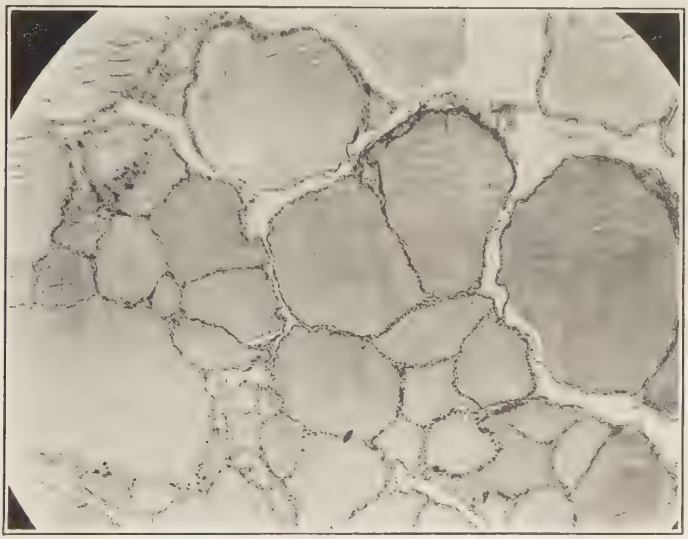

FIG. 10.—Colloid storage phase of physiological activity. Large vesicles lined with low cuboidal epithelial cells and completely filled with uniformly staining colloid material.

In the resting phase the cells are larger, the cytoplasm is faintly granular, the nuclei show chromatic figures, and the vesicles are smaller and contain vacuolated colloid, which stains unevenly.

In the transition from the resting to the secretory phase the epithelial cells pass through three distinct stages: (1) the granular stage, in which the cytoplasm is filled with coarse granular bodies of two varieties—fine rods and dots; (2) the

vacuolar stage, in which the vacuoles appear in the cytoplasm and migrate toward the lumen of the vesicle; and (3) the lacunar stage, in which the vacuoles coalesce and are extruded or blend with the vesicular contents.

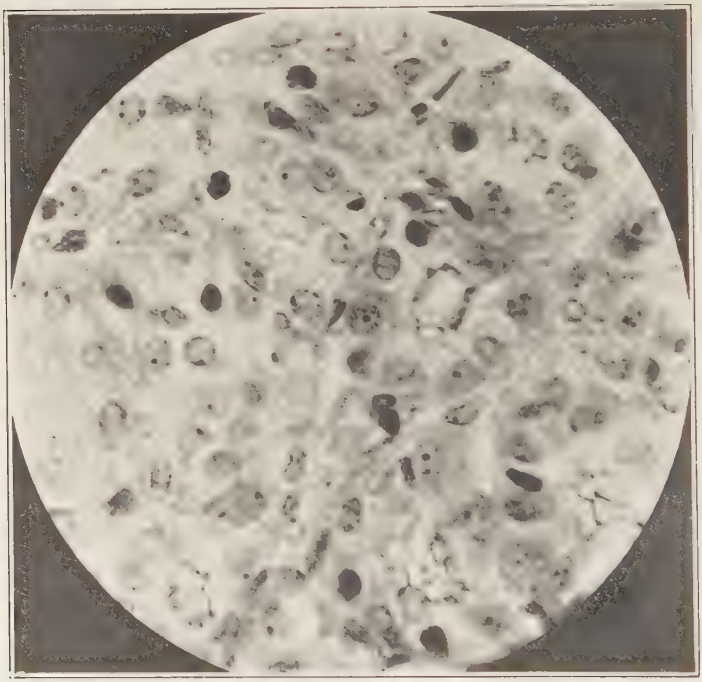

FIG. 11.—Intermediate or resting stage. Distinct microcapillary systems, about which epithelium is arranged in rings; two types of epithelial nuclei, (*a*) smaller, oval, deeply staining, and (*b*) larger, circular and pale; granular cytoplasm; no colloid in vesicles.

In the secretory or excretory phase the perivesicular spaces are dilated with a clear fluid and crowded with lymphocytes. The epithelial cells are high-columnar in form and contain either coarse granules or vacuoles or both. The nuclei migrate toward the pole farthest away from the lumen of the vesicle. The vesicles are small and contain no stainable material. Williamson and Pearse think that the

thyroid hormone is formed in this third phase, the colloid being regarded as a vehicle analogous to bile. Others look upon it as the stage of excretion, in which the colloid is liquefied and absorbed into the blood stream.

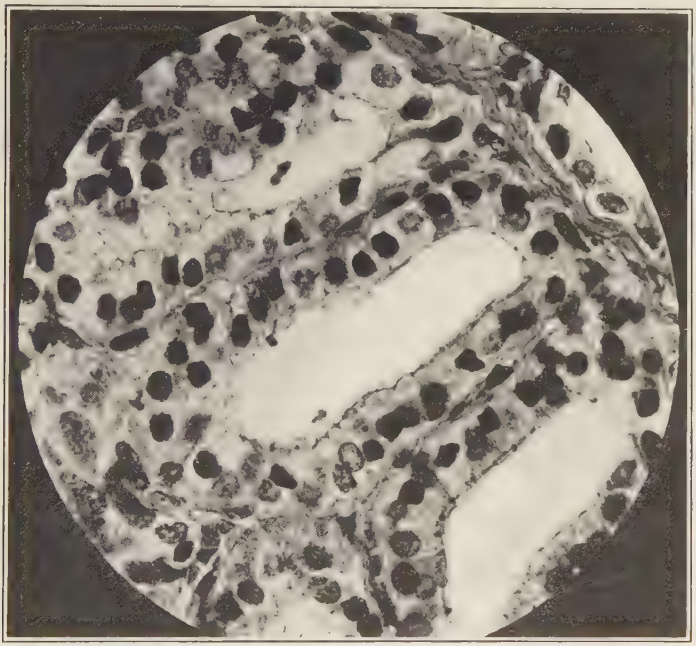

FIG. 12.—Secretory phase. No stainable colloid; vesicles irregular in shape; endothelial activity in interacinar spaces; increase in f.c.t. Epithelium columnar. Nearly all nuclei dense and darkly staining. Granular cytoplasm. Prominent microcapillaries.

Williamson and Pearse have described microcanaliculi embedded in the cells of the epithelial column. These structures are demonstrable only by special methods of tissue fixation and their appearance varies with the phase of glandular activity. In the colloid storage phase they are just visible as fine segmented lines, immediately beneath the surface of the cytoplasm, each segment corresponding to the individual epithelial cell. Nodal enlargements occur at

points of junction or intersection with other microcanaliculi. In the intermediate or resting phase the canaliculi are of larger caliber and unite with each other to form a network, in appearance not unlike chicken wire. In the secretory phase the canaliculi are of still larger caliber, stain deeply, and contain granular material. These microcanaliculi are thought to be the channels of absorption through which the internal secretory products are conducted to the interlobular lymphatics. Similar structures in the tissues of other organs have been demonstrated by Williamson's methods of fixation and staining. Doubt has been cast upon the existence of these so-called canaliculi and therefore upon their function as radicals of the thyroid lymphatic system. The question is whether these structures are definite anatomical entities with a specific function or whether they appear in the preparations merely as the result of the fixative employed (Figs. 10, 11 and 12).

Kittleisten, an intercellular cement substance demonstrable in certain tissues by silver impregnation methods, has a distinct resemblance to the microcanaliculi of Williamson and Pearse.

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CHAPTER III.

PHYSIOLOGY OF THE THYROID GLAND.

A NORMALLY functioning thyroid gland is essential for body development and the control of those physical and chemical activities which constitute general metabolism. For normal function the thyroid requires a definite supply of iodine. The actual amount, however, has not yet been determined.

There are two main phases in physiological activity: (1) the storage phase, in which colloid is formed and stored in the vesicles; and (2) the secretory or excretory phase, in which fluid substances other than colloid are elaborated and released into the lymphatics or blood capillaries. There is also a resting phase after each of these.

All parts of the gland are believed to participate at some time in both the colloid storage and the secretory phase. In the fasting animal about 98 per cent of the total gland volume is in the colloid storage phase, the remaining 2 per cent in the secretory phase. Eason has shown that the percentage of secretory tissue is much increased in animals after feeding.

The storage of colloid continues throughout life, unless there is complete failure of iodine supply.

The thyroid gland, unlike other parenchymatous organs, contains a considerable quantity of iodine; in a normal gland of average size there is from 5 to 6 mg., the concentration varying in different specimens. There is less in infancy and old age than in adult life, and generally more in the male gland than in the female. Most of this iodine is found in the colloid material. Feeding experiments indicate that the

iodine content of the gland increases when large quantities of iodine are ingested.

The fluid substances produced in the secretory phase are conveyed into the circulation, through which they are transported to all tissues of the body. They are thought to have at least two functions:

1. The promotion of development and growth. This function they share with the pituitary, the thymus, the suprarenal cortex, and the genital glands. While thyroid secretion influences the growth and development of all organs and tissues, it affects most actively the nervous system, the growth areas in bone and the genital glands.

2. Regulation of the physico-chemical processes in all tissues (metabolism). It is thought that, under normal conditions, the thyroid supplies each body cell with a hormone which acts as a catalyst, confining the physico-chemical processes of the cell within normal limits and controlling the rate of oxidation. It has been amply proven that, if after a fast of twelve hours the body be placed at rest for one hour, the physico-chemical activities (heat production and carbon dioxide elimination) which result from respiration, circulation, secretion, and muscle tonus – in other words the activities of the primary functions – become constant per unit of time, per kilogram of body weight, and per square meter of body surface. This rate of energy exchange is called the basal metabolic rate.

Metabolism is now generally estimated by indirect calorimetric methods. In healthy people the basal metabolic rate, expressed in percentages, ranges between 10 per cent below and 10 per cent above normal mean.

While the secretory products of the thyroid have never been isolated from the general circulation, Lunde is of the opinion that the alcohol-insoluble organic fraction of iodine (albumin iodine) in the blood contains the active principle of thyroid secretion. Lunde's view is based upon his observa-

tion that the alcohol-insoluble organic fraction of iodine in the blood of patients with untreated exophthalmic goiter is always increased and that with its decline under iodine treatment there is a parallel and coincident decrease in the basal metabolic rate and the symptoms.

Several products have been isolated from the thyroid gland. Chief among these are:

1. Albuminoid substances.
   (*a*) Iodothyrine (Bauman).
   (*b*) Iodothyroglobulin (Oswald, 0.15 per cent iodine).
   (*c*) Nucleoprotein (Oswald, contains no iodine).
2. Non-albuminoid substances.
   (*a*) Thyroglandol (Hoffman and Laroche).
   (*b*) Thyroxine (Kendall and Harrington).

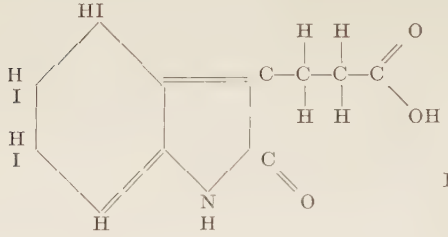
There are available more accurate data upon thyroxine and iodothyrine than upon the other thyroid derivatives.

Kendall separated iodothyrine from desiccated thyroid by the method of Bauman and found that it contained 4.6 per cent of iodine and possessed typical thyroid activity, abolishing the hypothyroidism of thyroidectomized animals as effectively as did the whole gland product from which it was extracted.

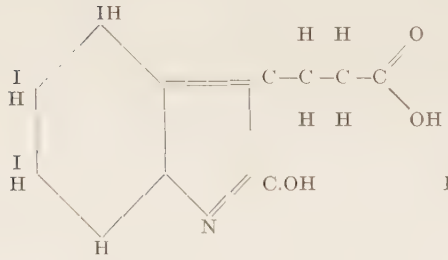
Of the non-albuminoid substances thyroxine is the best known. It is a crystalline protein compound, with high iodine content (65 per cent). If administered to normal animals, it produces symptoms of hyperthyroidism. If given to completely thyroidectomized animals, it prevents the development of cachexia thyreopriva. One-third of a milligram raises the basal metabolism of a normal person weighing 150 pounds by 1 per cent. In a case of myxedema with a rate of −30 the administration in a single dose of 10 mg. of thyroxine will bring the basal metabolic rate to normal within ten or twelve days. The rate will then remain approximately normal for ten days, gradually declining to −30 in from five to seven weeks.

KENDALL FORMULA FOR THYROXINE.*

4. 5. 6. tri hydro, 4. 5. 6. tri iodo, 2 oxy. beta indol propionic acid



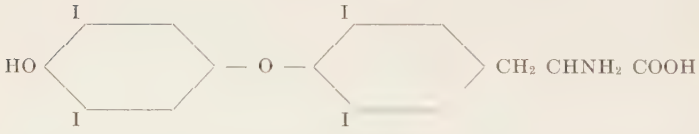
Keto Form



Enol Form

HARRINGTON FORMULA FOR THYROXINE.†

B (tetra iodo P. hydroxy-diphenyl ether) alanine



Within recent months Kendall has endeavored to determine the thyroxine content of thyroid gland preparations. All the samples tested were proven to be physiologically active, and the iodine content of some of them was above the average. Yet from practically none could thyroxine be obtained. Kendall's conclusion was that thyroxine is an intermediate product in the formation of "active thyroxine," which is the

* Jour. Biol. Chem., 1919, **39**, 125.

† Harrington and Barger: Biochemical Jour., 1926, **20**, 293, 300.

true functioning principle of desiccated thyroid products. Although the chemical composition of "active thyroxine" is still unknown, Kendall suggests that the conversion of thyroxine into "active thyroxine" may be effected by the addition of a second hydroxyl group to the outer benzene ring of thyroxine.

While qualitatively thyroxine is the same as "active thyroxine," quantitatively it is less potent. The transformation of the stable crystalline element into the unstable but more active element can be effected by the tissues of a thyroidless animal. It occurs also in thyroid tissue during the process of desiccation. Should the comparative quantitative action of these two compounds be established, it is possible that the following conclusions regarding the physiological action of thyroxine may come to be expressed in terms of "active thyroxine."

The body, exclusive of the thyroid gland, contains normally about 14 mg. of thyroxine. The daily consumption of thyroxine is between 0.5 and 1 mg., average 0.75 mg. Plummer believes that, when the amount of thyroxine in the body tissues falls below normal, the release of thyroxine from the thyroid into the blood stream is stimulated. An increase or decrease of 1 mg. of thyroxine in the body tissues is accompanied by a corresponding rise or fall of from 2 to 5 per cent in the basal metabolic rate.

The thyroid gland possesses great elasticity of function, which as a rule enables it to sustain without permanent derangement the accelerated metabolism coincident with puberty, menstruation, gestation, and the menopause, as well as that induced by excessive muscular exertion or acute infections associated with fever. Under such stress the gland may temporarily become larger and firmer, without the development, however, of abnormal secretory activity or permanent structural change.

It has been thought by many, and the view has found some support in experimental and clinical observation, that the

thyroid secretion possesses antibacterial and antitoxic properties. More recent research, however, has failed to establish conclusive proof of such function.

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CHAPTER IV.

PATHOLOGICAL PHYSIOLOGY.

Abnormal thyroid function may be due to either a congenital or an acquired defect. The gland may be absent, or it may possess such limited functional capacity that it cannot meet the ordinary demands of growth and development. On the other hand, its function may be accelerated or perverted because of iodine shortage, polluted water, rapid growth, pregnancy, infection, or excessive physical or mental strain. Or again its function may be curtailed or destroyed by inflammation or as a result of surgical removal.

There are three types of abnormal secretory activity:

1. Hypothyroidism, in which the secretion is normal in quality, but insufficient in quantity.

2. Hyperthyroidism, in which the secretion is normal in quality, but excessive in quantity.

3. Dysthyroidism, in which the secretion is abnormal in quality as well as excessive in quantity.

In cretinism, an endemic disease characterized by dwarfism and mental deficiency, we have a congenital insufficiency of secretion (hypothyroidism). The administration of thyroid extract stimulates growth, lessens the mental lethargy and improves the general nutrition.

Partial destruction of the gland by inflammation may result in hypothyroidism, manifested by a general doughy swelling of the face and hands, mental dulness, thick or retarded speech, slow movements, digestive and menstrual disturbances, sensitiveness to cold, pallor, and a subnormal basal metabolism.

Surgical removal of the whole gland or complete destruction by inflammation also induces hypothyroidism. The clinical picture varies with the age of the patient. In young

subjects ossification in the epiphyses is retarded, growth arrested, and puberty suppressed or delayed. In adults anemia develops, with a firm edema of the skin (myxedema). The hair becomes dry and coarse and generally much thinner. The basal metabolic rate may fall as low as −50 per cent. The mental faculties are dulled. At first the weight increases and there is a positive nitrogen balance. Later, however, if no treatment is instigated, there is a negative nitrogen balance, with loss of weight, emaciation, progressive anemia, increasing weakness and death. In the early days of thyroid surgery this condition was often seen. It was designated as "Cachexia strumipriva" by Kocher; "Cachexia thyreopriva" by others; and was often associated with varying grades of tetany due to coincident removal of or injury to the parathyroid glandules. The development of cachexia thyreopriva following extirpation of the gland in man or animals is prevented by the administration of gland preparations, which are also effective in curing the condition. Thyroxine administered intravenously is said to possess all the physiological properties of the dried gland.

In non-toxic adenoma (nodular goiter without hyperthyroidism) the gland remains physiologically normal, producing the required amount of hormone, which is distributed and used in the body at the normal rate.

In toxic adenoma, a disease more prevalent in America than in other countries, the status is apparently that of a pure hyperthyroidism. The symptoms are almost identically the same as those produced in man and animals by the administration of thyroxine or thyroid gland preparations, although the frequent coincident myocardial changes and hypertension suggest that a toxic element is also present. Removal of the adenomatous tissue abolishes the toxicity, brings the basal metabolic rate to normal, and not infrequently, especially in those cases in which there are no permanent changes in the circulatory apparatus, lowers the blood pressure. The uniformly satisfactory effects of resection suggest that the

secretion causing the thyrotoxicosis is derived from the adenomatous tissue.

In some cases of malignant disease of the thyroid there is definite hyperthyroidism. Observations in the Montreal General Hospital Clinic, as well as those of von Recklinghausen, von Eiselsberg, and others, suggest that even metastatic implants may elaborate a secretion simulating that of the normal thyroid and that this secretion may satisfy physiological demands after the parent gland has been removed.

Adolescent or juvenile goiter is not usually accompanied by a disturbance of gland physiology. The basal metabolic rate is normal and there are no clinical symptoms. If, however, the iodine insufficiency in the food and water is unrelieved and such factors as inadequate rest, physical strain, or infection should be superimposed, or iodine be administered in excessive dosage, symptoms of hyperthyroidism may develop, manifested in tachycardia, nervousness, tremor, loss of weight, loss of energy and increased heat production.

In the early stages when nervousness and tachycardia are the main symptoms, Graves' disease is indistinguishable from true hyperthyroidism. But, when the disease is fully established, there appear symptoms (exophthalmos, for example) which have not been produced in man or animals by the administration of desiccated thyroid or thyroxine, and which cannot be attributed to simple hyperthyroidism. For this reason the established disease is thought to be a dysthyroidism. By this is meant that the thyroid secretion is, to a certain degree, qualitatively abnormal as well as excessive, and acts as a toxin. The hormone may be deformed or defective, or the secretion may not be conveyed at a normal rate or through the proper channels, and may become altered as the result of stagnation or diversion. It is thought that, as fibrosis advances, the pent-up secretion escapes into the circulation through the capillaries rather than through the lymphatics.

The pathological physiology of the cardiovascular system in Graves' disease is not difficult to understand. The heart muscle is, with the other organs, stimulated by the increased hormone supply, but still more important is the acceleration of the heart's action in response to the increased body demands. Each body cell, owing to its augmented metabolism, needs an increased oxygen supply, and to meet this need the output of the heart must be raised. This is effected at first by an increase in the heart rate; later, most probably, by an increase in the stroke volume—a sequence of events which contrasts with the early increase in stroke volume and the later tachycardia in ordinary muscular effort. The fairly frequent clinical observation of a falling pulse with the maintenance of the basal metabolic rate at a high level supports this view.

The prolonged tachycardia brings in its train inevitable consequences—loss of cardiac reserve, loss of efficiency even when the patient is at rest, and ultimately myocardial degeneration.

The cause of exophthalmos is not definitely known. The following explanations are worthy of note:

1. Contraction of the musculus orbitalis (muscle of Müller). This is a narrow band of involuntary muscle fiber bridging the inferior orbital fissure. It is innervated by the sympathetic system. In animals in which this muscle was well developed, Müller found that irritation of the cervical sympathetic produced exophthalmos, and in such animals he was able also to demonstrate an antagonist the retractor bulbi muscle. Krauss and Frund believe that in man exophthalmos results from a combination of the protractor action of the musculus orbitalis and orbital engorgement due to direct pressure of the muscle on the ophthalmic veins, with retardation of the venous circulation. But, since in man the muscle is vestigial, and the excitation of the nerve does not lead to exophthalmos (Turner), this explanation does not seem very acceptable. Hesser studied the venous circulation carefully,

and only in exceptional cases did he find either the superior or the inferior ophthalmic vein in a position where it could be affected by the contraction of this muscle. Furthermore, the free anastomosis between the veins of the orbit and those of the face would prevent venous engorgement.

2. Contraction of the periorbital involuntary musculature, the musculus capsulo-palpebraris, a scattered and ill-defined layer of smooth muscle fibers associated with the fascia bulbi (Tenon's capsule) and innervated by the sympathetic.

Anteriorly it extends into the eyelids, forming the palpebral involuntary muscle of Müller, which should not be confused with the musculus orbitalis already referred to. Landstrom considered contraction of this sheet of muscle fibers to be the cause of exophthalmos.

3. Retraction of the lid (Stellwag's sign) through the action of the levator palpebræ superioris.

This action probably permits more readily the advancement of the eyeball. In early cases of Graves' disease one often observes a protrusion of the eyeball as the lids are opened and a recession as they are closed.

4. Loss of tone in the recti muscles.

5. Dilatation of the orbital bloodvessels by excitation of the sympathetic nervous system.

Fuchs came to the conclusion that this was the most probable cause.

6. Edema of the orbital tissues (Sättler). This is undoubtedly a transitory factor in certain cases.

Though only one thyroid lobe be enlarged, the exophthalmos is usually bilateral. Not uncommonly one eye protrudes sooner than the other, and in these cases the eye which first became prominent is the last to recede. In practically all early cases and in many chronic cases cure of the disease results in the disappearance of the exophthalmos. The deposit of retro-orbital fat in later stages is thought to be responsible for the persistence of exophthalmos after the exciting cause has been removed.

Unilateral exophthalmos is difficult to explain.

Glycosuria or hyperglycemia associated with Graves' disease or toxic adenoma may be due to:

1. True diabetes mellitus. Lattler reports 40 cases associated with Graves' disease.

2. The ingestion of excessive quantities of carbohydrates (alimentary glycosuria).

3. Low renal threshold (renal glycosuria).

4. Defective storage of carbohydrates in the liver, directly due to the hyperthyroidism.

Glycosuria due to hyperthyroidism is not the result of defective insulin production, nor is it the result of defective oxidation of sugar. As a matter of fact, an individual with hyperthyroidism can and does oxidize sugar more rapidly than does a normal individual. The abnormal condition here is defective storage, probably due to excessive quantities of adrenalin in the blood. The adrenalin theory has been questioned, but no better one has yet been offered, and there is much indirect evidence (experimental) in favor of it.

Abnormal metabolism of carbohydrates in hyperthyroidism is suggested from the results obtained in blood sugar time curves. These show that, following the ingestion of glucose, the blood sugar may rise to a much higher level than is normal (diminished tolerance). According to Schulze this rise occurs in 25 per cent of cases of toxic goiter, and according to Bram in 85 per cent. If there is a marked disturbance, the blood sugar may fail to return to the normal level within the usual time, namely, two and a half to three hours (delayed assimilation).

Finally, the general physiology may be adversely affected by pressure from an adenomatous growth. Deviation or compression of the trachea may cause respiratory distress. The great veins of the neck may be compressed or occluded, or may become thrombosed. Pressure upon the recurrent laryngeal nerve may cause paralysis of a vocal cord and impaired phonation. Pressure upon the cervical sympathetic

cord may result in ptosis, enophthalmos and myosis in the homolateral eye. If the goiter becomes fixed, deglutition may be interfered with and normal laryngeal movements restricted.

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CHAPTER V.

PATHOLOGY: GROSS AND MICROSCOPIC.

Until more is known about the etiology of thyroid lesions, any pathological classification must necessarily be a makeshift. Except in the case of Graves' disease we have not even approached the point where the symptomatology and pathology can be shown to be in any way correlated. For example, the clinical differentiation between non-toxic and toxic adenomata is unsupported by any demonstrable difference in the gross or histological pathology, unless one accept Goetsch's view that an excessive production of the cell mitochondria constitutes a histological factor common to both Graves' disease and toxic adenoma, distinguishing the latter from non-toxic nodular goiter. A descriptive classification seems to us the best that can be offered at the present time, but even this is put forward rather as a counsel of desperation.

The following classification, in so far as it refers to trophic and plastic lesions, is that suggested by Williamson and Pearse, and, although not generally accepted on this continent, has in our experience proved a satisfactory working basis. Here the term "hyperplasia" is restricted to those lesions which are characterized by a balanced overgrowth of all tissue elements, while the term "adenoid heterotrophy" is given to the lesion of Graves' disease — the only lesion where there exists a definite and constant relation between the clinical symptoms and the pathological findings.

Classification.

I. *Trophic Changes:*
1. Hypertrophy.
   (*a*) Physiological.
   (*b*) Pathological.
2. Heterotrophy.
   (*a*) Colloid or vesicular.
   (*b*) Adenoid ("hyperplastic" of American literature).

II. *Plastic Changes:*
1. Hyperplasia (balanced overgrowth).
   (*a*) Simple.
   (*b*) Lymphadenoid.
2. Heteroplasia.
   (*a*) Perivesicular fibrosis.
   (*b*) Perilobular fibrosis.

III. *Inflammations:*
1. Thyroiditis.
   (*a*) Simple.
   (*b*) Ligneous.
   (*c*) Suppurative.
   (*d*) Specific.
      Syphilitic.
      Actinomycotic.
      Tuberculous.
         Miliary.
         Caseo-suppurative.
         Lardaceous.
      Parasitic (Chagas' disease).
2. Strumitis.
   (*a*) Simple.
   (*b*) Suppurative.
   (*c*) Specific.

IV. *Neoplasms:*
1. Benign.
   (*a*) Fetal adenoma.
   (*b*) Adult adenoma.
   (*c*) Langhans' proliferating adenoma.
2. Malignant.
   (*a*) Malignant adenoma.
      Fetal.
      Adult.
      Papillomatous.
   (*b*) Carcinoma.
      Simple.
      Medullary.
      Scirrhous.
   (*c*) Epithelioma.
   (*d*) Endothelioma.
   (*e*) Sarcoma.

The most distinctive feature of thyroid pathology is the occurrence of trophic or plastic lesions which are subject to extensive progressive or retrogressive secondary change. Upon examination of a gross specimen and its histological preparation it may be possible to retrace the various structural phases through which the tissues have passed.

The conception of disease as primarily an exaggeration and secondarily a perversion of physiological activity, resulting ultimately in a restriction or abolition of function and

accompanied as a rule by structural change, applies with special force to the thyroid gland.

Two points in the pathology of the thyroid should be emphasized:

1. That in the same goitrous gland one may find an astounding variation in structure. An area of apparently normal tissue may be in close relation with an area of malignant tissue, while in other fields as a result of inflammatory, degenerative or regenerative changes, the tissue structure may simulate that of hypernephroma or even that of malignant neoplasm, without either of these conditions being actually present. To avoid an erroneous diagnosis, therefore, the microscopic examination should be comprehensive and cover sections from several segments of the specimen.

2. That a fine or coarse fibrosis is very often induced in the thyroid by "tissue strain" (Adami), and is the chief cause of the variety of lesions met with. A fine fibrosis isolates individual vesicles and limits or destroys their secretory activity. A coarse fibrosis may isolate whole lobules, causing them to perish from lack of nutrition. On the other hand, if nutrition be maintained, overgrowth may follow.

HYPERTROPHY OF THE THYROID GLAND.

Hypertrophy is an increase in the size of individual cell units, without an increase in their number. It may be either physiological or pathological.

(*a*) **Physiological.**—This is a uniform, soft enlargement of the gland, due to vascular increase, but without the formation of new tissue, occurring at certain periods—puberty, menstruation, pregnancy and the menopause. There are no clinical symptoms, neither is there deranged function. Histologically the tissue is normal and the normal relation between the colloid storage phase and the secretory phase is maintained.

(*b*) **Pathological.**—This is a simple enlargement with maintenance of the relative proportions of colloid storage and secreting tissue, which is, however, not a response to a normal physiological demand. There are definite clinical symptoms. Williamson includes in this class the goiter of status lymphaticus.

HETEROTROPHY OF THE THYROID GLAND.

A nutritive or trophic disturbance, where one phase of glandular activity is grossly exaggerated and the other is normal or suppressed. There are thus two possible types of heterotrophic goiter: (*a*) colloid or vesicular, and (*b*) adenoid (the hyperplastic goiter of American authors), the latter being the lesion in Graves' disease.

(*a*) **Colloid or Vesicular Goiter.**—If the storage of colloid completely overshadows the secretory function, the vesicles become distended with colloid material and the gland enlarges, the lesion being designated clinically as colloid goiter. Grossly the gland is soft in consistence and smooth in appearance, except where it has been subjected to pressure; cystic and adenomatous formations are frequent, and degenerative changes ranging from dense fibrosis to calcification are met with. The outstanding histological feature is the presence of distended colloid vesicles. No active secretory tissue is demonstrable. The epithelial cells are flattened; their nuclei stain diffusely, but faintly. The cytoplasm is clear. The microcapillaries are narrow and contain no granules.

(*b*) **Adenoid Goiter.**—This is the characteristic lesion in Graves' disease. The epithelium is uniformly involved in the secretory phase, the three stages of which (granular, vacuolar and lacunar) may be seen. Colloid storage is absent. The epithelial cells are swollen and high-columnar in form, and are infolded into the vesicular spaces. The cytoplasm is granular. The nuclei are peripheral. The

lymphatics are crowded with mononuclear lymphocytes. There is proliferation of the endothelial cells lining the lymph spaces. The blood capillaries are dilated. The microcapillaries are large and distinct, and contain a granular substance.

In the early stages of adenoid goiter there is, in many instances, little increase in tissue volume. There is no fixed relation between the degree of toxicity and the degree of thyroid enlargement. Indeed, a rapidly fatal form of the disease may develop without demonstrable increase in the size of the gland.

In chronic cases striking histological changes may be noted. The first of these is a fine interlobular fibrosis. Later the epithelium isolated by this fibrosis becomes exhausted and loses its secretory appearance; the vesicles become distended with a clear unstainable substance, which is not colloid. In the advanced stages parts of the gland may atrophy and give place to scar formation. If, however, the condition subsides spontaneously, is controlled by iodine medication, or is arrested by operation, vasodilatation and lymph-cell invasion disappear, and the normal proportions of secretory and colloid storage tissue are reëstablished. This is the process of involution. Involution, however, does not necessarily proceed uniformly throughout the gland. Some areas may show rapid involution, with the formation of localized collections of vesicles distended with colloid (hyperinvolution), while in others secretory tissue may preponderate (hypoinvolution) (Fig. 13).

Many studies have been made of the effect of iodine on the thyroid structure of patients with exophthalmic goiter. The outstanding result is an increase in the colloid content of the gland. Other changes, such as an increase in stroma, a decrease in vascularity, and alteration in cell form, have been described, but these findings are inconstant. Reinhof reports having removed gland tissue before commencing the iodine treatment of cases of Graves' disease. He

then gave iodine to these patients and later removed the goiters. He described many structural changes, even attributing to these changes the origin of adenomatous growths. Hellwig was unable to confirm Reinhof's work.

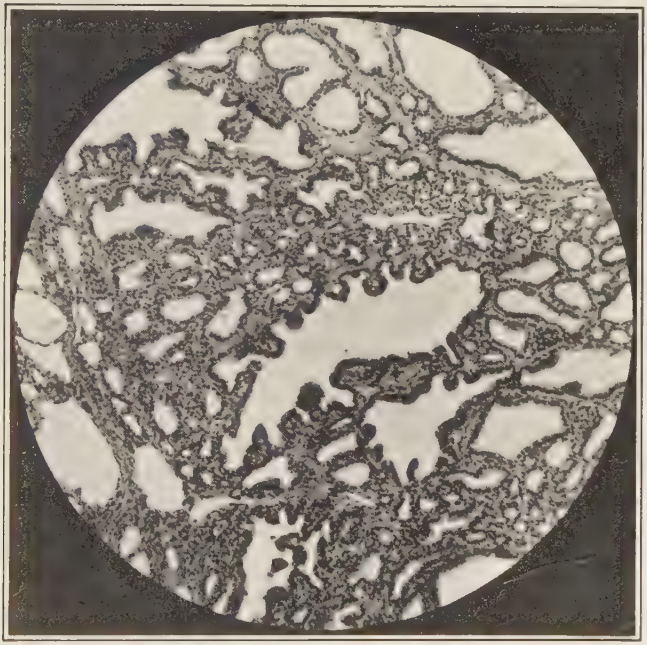

FIG. 13.—Adenoid goiter, the tissue of Graves' disease. Papillary infoldings are prominent.

Smith, Clute and Strieder have described large atypical cells, usually lining small acini and showing an intense acidophilic staining reaction of the cytoplasm. These atypical cells have been found especially in cases in which myxedema followed operation.

In trophic changes increase in the size of the gland is primarily nutritional, new tissue growth occurring as a

secondary change. There are, however, goiters in which there is a plastic increase in the glandular tissue from the beginning of the enlargement.

HYPERPLASIA OF THE THYROID GLAND.

The term "hyperplasia" is used here in its limited pathological sense, to designate a balanced overgrowth of all tissue elements. Hyperplasia also implies a certain degree of hypertrophy. While the line between hypertrophy and hyperplasia is indistinct, often indefinable, there is, nevertheless, a true difference; and among the pathological lesions of the thyroid one meets with instances in which the balanced overgrowth of the tissues must be interpreted as an attempt to augment by growth the secretory output of a gland already taxed to its functional limit.

There are two ways in which the thyroid gland may be inadequate: (1) anatomically, the volume of secretory tissue being too limited for the increased demands of the body under the stress of physiological hyperactivity (straining gland), and (2) physiologically, the physiological capacity of the gland being impaired, though sufficient gland is present. In the latter type physiological activity may be at its lowest level (sluggish gland).

In either type hyperplasia may develop, that is an overgrowth of tissue to compensate for an anatomical or physiological insufficiency.

(*a*) **Simple Hyperplastic Goiter.** Examination of the gross specimen shows a large gland, in which there is a diffuse perilobular fibrosis (strain fibrosis). Embedded in the parenchyma are a variable number of encapsulated nodes, which on gross section closely resemble hypertrophic tissue. They are in fact local hypertrophies.

Microscopically there is seen thyroid tissue in various stages of activity, but there is a relative increase in the amount of tissue in the secretory phase. Colloid, however, is always

present. Limited degenerative changes often occur. It is probable that many of the nodular goiters described as toxic adenomata have their origin in lesions of this nature. It is also reasonable to assume that true neoplasms, benign or malignant, may arise in such tissue. That they arise in

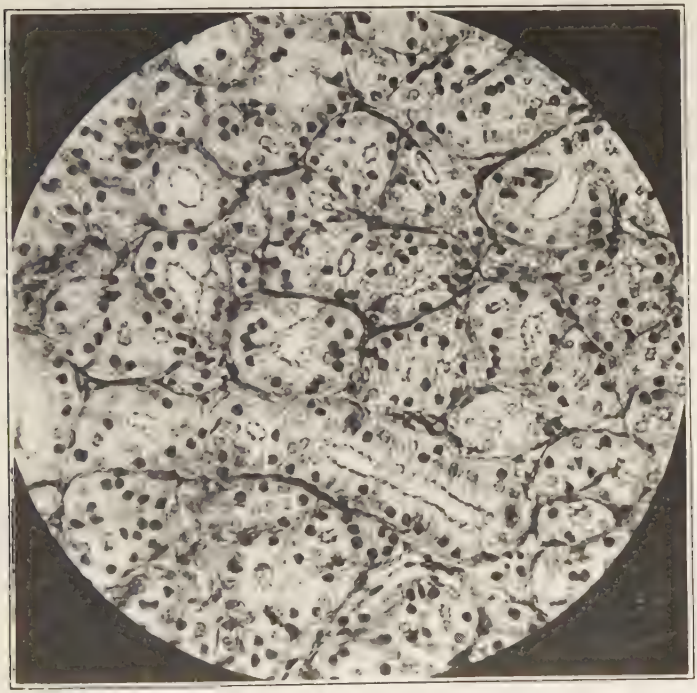

Fig. 14.—Perivesicular fibrosis.

comparable lesions of the mammary gland, prostate, and ovary, has apparently been proved beyond question.

It is further evident that, if such an encapsulated mass is overlooked at operation, its continued growth may give rise to a recurrence of the clinical symptoms.

In view of the present trend of cancer research, the connection between this focal form of gland hyperplasia and true neoplasia is, of course, of great interest.

(*b*) **Lymphadenoid Goiter.** This is hyperplasia in a physiologically subnormal gland. This lesion has not yet been

FIG. 15.—Perilobular fibrosis.

finally classified. It has been called ligneous thyroiditis or iron-hard strumitis by European authors, benign granuloma by Ewing, and chronic thyroiditis by pathologists generally. Pending further knowledge we have included it in the inflammatory lesions.

HETEROPLASIA OF THE THYROID GLAND.

Heteroplasia means unbalanced overgrowth. In the thyroid this process manifests itself as a progressive fibrosis of the interstitial tissues.

FIG. 16.—Heteroplasia, advanced stage, showing irregular scarring with the inclusion of areas of gland tissue.

(*a*) **Perivesicular Fibrosis** (the European arterio-capillary sclerotic goiter) is comparable to primary interstitial nephritis or pericellular cirrhosis of the liver. This lesion often complicates the hypertrophic or hyperplastic forms of goiter. As the fibrosis proceeds, the lymph channels of the vesicle-

become obstructed and absorption of the stagnant and toxic secretion takes place through the capillaries (Fig. 14).

(*b*) **Perilobular Fibrosis.**—This is the commonest form of pathological change found in goitrous glands. It is analogous to perilobular cirrhosis of the liver. The strain of excessive physiological activity or the toxins of infection may induce in the perilobular interstitial tissue a progressive fibrosis. This in turn may lead to the formation of small retention cysts, or an active overgrowth in the isolated areas of epithelium, which may go on to the formation of adenomata. Adenomata developing as the result of this form of tissue change are often of the fetal type. Later, as the result of vascular compression, various degenerative lesions occur—atrophy, hyalin change, cyst formation, calcification, or massive scarring. Minute hemorrhages are also frequently seen. At the same time hypertrophy or hyperplasia may occur in other parts of the gland, producing a very complicated picture (Figs. 15 and 16).

INFLAMMATIONS OF THE THYROID GLAND.

Inflammations of the thyroid gland are classified as follows:

I. *Thyroiditis:*
- (*a*) Simple (toxic)
- (*b*) Ligneous
- (*c*) Suppurative
- (*d*) Specific
  - (1) Syphilitic
  - (2) Actinomycotic
  - (3) Tuberculous
    - (*a*) Miliary
    - (*b*) Caseo-suppurative
    - (*c*) Lardaceous
  - (4) Parasitic (Chagas' disease)

II. *Strumitis:*
- (*a*) Simple (toxic)
- (*b*) Suppurative
- (*c*) Specific

Thyroiditis. - Thyroiditis is an inflammation developing in a normal gland. It may be simple, ligneous, suppurative, or specific.

(*a*) Simple or Toxic. On gross section the gland shows either a diffuse fibrosis or isolated areas of scar tissue. His-

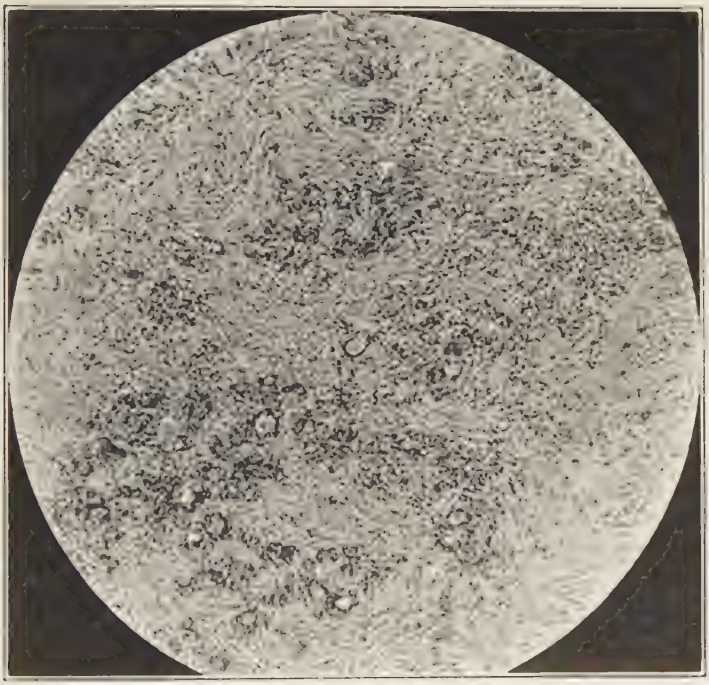

Fig. 17.—Simple thyroiditis. Replacement fibrosis with compression atrophy of the few remaining vesicles.

tologically the parenchyma is seen to be supplanted by an extremely dense homogeneous scar tissue in which are embedded a few wandering lymphocytes and the nuclei of epithelial cells (Fig. 17).

(*b*) Ligneous Thyroiditis (Delore and Mamartine), iron-hard strumitis (Riedel), benign granuloma (Ewing).

Williamson looks upon this lesion as a replacement fibrosis following exhaustion and atrophy in hyperplasia of a physiologically subnormal gland. He describes it under the title of lymphadenoid hyperplasia.

It is Williamson's claim that this lesion develops in a gland in which a prenatal fault or postnatal damage by infection has produced a curtailed or impaired physiological capacity. As the individual grows or if the gland is further injured by infection, there is insufficient elasticity of function to meet even minimal requirements, and as a result hyperplasia occurs.

Grossly there is an intensely hard enlargement, general or local, and as a rule extension of the fibrosis to the surrounding structures. The surface of the gland is smooth or granular.

We owe to Ewing the modern histological conception of the lesion. Under the name "benign granuloma" he connected the later stages described by Riedel with the earlier stages first noted by Hashimoto. Subsequent observations have supported his belief that the two pictures are but different phases of a continuous process. Microscopic sections from a goiter of this kind in the early stages may show both colloid storage and secretory activity, but the predominating feature is universal lymphocytic invasion, filling the distended lymphatics and forming many germinal centers. There is also a diffuse infiltration with plasma cells and eosinophiles. Gradually the colloid disappears and for the greater part the epithelial cells enlarge and degenerate. The débris of these cells is removed by phagocytosis. In the late stage the alveoli collapse, and many of the remaining epithelial cells fuse and form giant cells. These giant cells are replaced by fibrous connective tissue, which ultimately undergoes hyalin change. The progressive sclerosis replaces first the epithelial elements, next the wandering cells (lymphocytes), and lastly the germinal centers. Persisting germinal centers may give the appearance of carcinoma. Surviving epithelium may hypertrophy and adenomatous

compensatory foci may develop—comparable to the compensatory regeneration in cirrhosis of the liver, and for this reason, although the parenchyma is extensively destroyed, myxedema is the exception. In cretins the same fibrotic replacement occurs, but without the compensatory hypertrophy (Fig. 18).

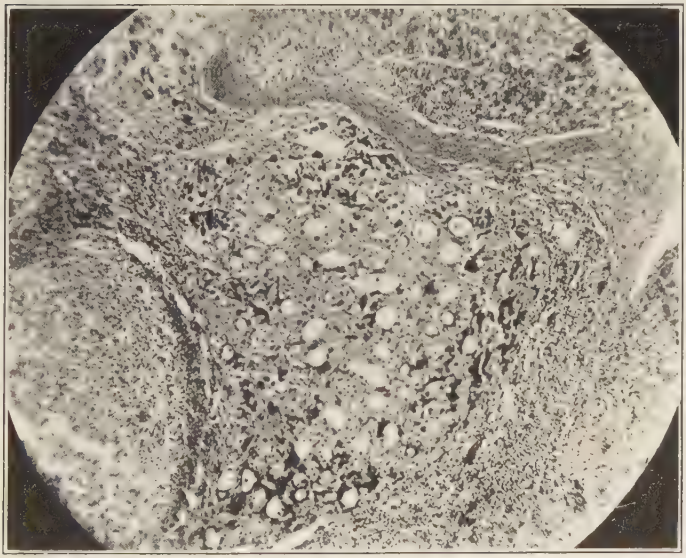

FIG. 18.—Ligneous thyroiditis, showing (1) lymph-cell invasion, (2) germinal centers, (3) plasma and eosinophilic cells, (4) epithelial degeneration and fibrosis.

(*c*) SUPPURATIVE.—Abscess formation rarely follows simple thyroiditis. It usually occurs in association with generalized infections such as pneumonia, typhoid fever, scarlet fever and puerperal fever, or as a metastatic infection from alveolar abscess, tonsillitis, or sinusitis. In the early stages the process is confined within the thyroid capsule, although there may be considerable induration of the surrounding tissues. Later, if suppuration spreads beyond the thyroid gland, deep

cervical phlegmon and mediastinitis may develop unless the abscess is incised, or ruptures externally, or internally into the trachea or esophagus.

(*d*) SPECIFIC.—1. *Syphilitic.*—In recent syphilitic infection a generalized swelling of the gland may occur. More frequently, however, the disease takes the form of multiple tertiary gummata. The consistence of the gland is hard, and the surface nodular. Malignant disease may be closely simulated. The histological structure is that of typical gumma.

2. *Actinomycotic* invasion of the thyroid gland is rarely met with. The lesion resembles that of actinomycosis in other organs.

3. *Tuberculous* disease affects the thyroid gland in three distinct ways:

(*a*) As miliary tuberculosis—part of a terminal infection.

(*b*) In the form of caseating or suppurating foci, which may involve one or both lobes.

(*c*) As a non-suppurating process in which the whole gland may be converted into a homogeneous "lardaceous" mass, similar to that sometimes seen in the kidney. The lobes are thin-walled and completely filled with a soft gray material resembling putty. The diagnosis is made by histological examination.

4. *Parasitic* (*Chagas' Disease*).—Parasitic thyroiditis, met with in South America, is part of a constitutional disease due to infection by the Schizotrypanum cruzi. It is transmitted to man and animals by the bite of an insect. The blood stream is infected and the thyroid, when involved, undergoes inflammatory destruction.

Strumitis.—Strumitis is an inflammation developing in a goiter. It should be borne in mind that malignant as well as benign goitrous enlargements may be the seat of inflammatory change.

(*a*) Simple (Toxic).—Simple inflammation may occur in any part of a goitrous gland. There is at first a swelling, due to inflammatory edema, with wandering-cell invasion, and later a fibrosis of varying degree.

(*b*) Suppurative.—Suppurative strumitis occurs in the course of or following acute infectious diseases (pneumonia, typhoid fever, scarlet fever, puerperal fever, or diphtheria) or is secondary to focal infection (alveolar abscess, tonsillitis, sinusitis, etc.).

It is most commonly met with in adenomatous goiter and affects not the normal parenchyma but the nodular growth. Usually a single adenoma is involved. It becomes distended with purulent material. There is an inflammatory edema of the neighboring structures. If the condition is not treated, the pus may break through the gland capsule, and either spread beneath the deep cervical fascia or rupture through the skin or into the trachea or esophagus. The goitrous tissue which was the original site of the inflammation becomes converted into a necrotic mass. Even though spontaneous evacuation occurs, sinuses may persist because of the retention of calcified material.

Chronic suppuration may develop within an encapsulated adenoma without giving rise to infiltration of the perithyroid tissues. The diagnosis of suppuration in such cases is made on the local signs and by puncture.

(*c*) Specific.—Cases of tuberculous strumitis have been described. The pathology is that of tuberculous processes elsewhere.

NEOPLASMS OF THE THYROID GLAND.

Neoplasms are classified as follows:

I. *Benign:*
- (*a*) Fetal adenoma
- (*b*) Adult adenoma
- (*c*) Langhans' proliferating adenoma

II. *Malignant:* (*a*) Malignant adenoma
(1) Fetal
(2) Adult
(3) Papillomatous
(*b*) Carcinoma
(1) Simple
(2) Medullary
(3) Scirrhous
(*c*) Epithelioma
(*d*) Endothelioma
(*e*) Sarcoma

Benign Neoplasms. – In a clinical sense the term "adenoma" is used to designate any nodular mass developing in the thyroid gland. In the pathological sense it should be limited to benign autonomous growths of glandular structure. In actual practice, however, it is often impossible to determine whether an encapsulated thyroid mass is a true autonomous neoplasm or simply a trophic or plastic increase in an encapsulated area of parenchyma. A parallel difficulty is met with in classifying nodules developing in the prostate and breast. There is evidence to support the view that what appears primarily to be a simple hyperplasia may assume in the thyroid gland the characteristics of autonomous growth.

There are few, if any, criteria upon which one may rely in differentiating true tumor growths from hyperplasia or hypertrophy. It has been suggested by Klose that the absence of elastic tissue in the stroma may be indicative of new growth, but the value of this evidence has not been established. Fundamentally there is only one distinctive characteristic of a neoplasm, namely, that it is autonomous, and so far no method has been devised by which one can demonstrate this microscopically.

A striking feature of thyroid pathology, in contrast with that of other glandular organs, is the frequency with which these adenomata occur. A careful search in almost any surgical specimen of the thyroid will reveal one or more areas

sharply defined from the surrounding tissue by a fibrous capsule.

According to their histological structure benign adenomata are conveniently classified as fetal, adult and proliferating (Langhans).

In microscopic adenoma the capsule is seen to be composed of a thin layer of connective tissue enclosing a zone of parenchyma. As the adenoma enlarges, the capsule thickens and the growth compresses the surrounding thyroid vesicles. Within the fibers of the capsule are arterioles and blood capillaries.

(*a*) Fetal Adenoma.—This is an encapsulated spherical mass of homogeneous thyroid tissue, dry and pale brown on gross section, made up of closely-packed plates or rings of well-nourished epithelial cells of the low-cuboidal type, with central circular nuclei. Beneath the capsule the gland tissue is well nourished and stains deeply. In the intermediate zone occasional vesicles may be seen, containing stainable (colloid) material and separated from each other by a delicate, though well-developed, fibrous connective-tissue stroma supporting many blood capillaries. Prominent microcanaliculi have been noted in some specimens. In the center of the adenoma regressive changes, such as edema, atrophy and fibrosis, are very common (Fig. 19).

(*b*) Adult Adenoma.—This is an encapsulated mass, spherical or ovoid in outline, of varying consistence. The smaller growths are homogeneous and pale brown, and contain visible colloid vesicles. Histologically the general structure resembles normal gland tissue. Lymphocytes and germinal centers are rarely seen. Epithelium in the secretory phase is seldom demonstrable. The tumor consists mainly of distended vesicles, lined with flat or low-cuboidal epithelium and filled with deeply-staining colloid.

There is, however, one type of adult adenoma which does not conform to this picture, that is the adenoma which develops in simple hyperplastic goiter. In this nodule the

epithelium is seen in both the colloid storage and the secretory phase, although the lymph-tissue elements are generally scanty.

The adult adenoma rarely attains a diameter of more than 1 cm. without undergoing degenerative changes. The commonest of these are edema; cyst formation – the cyst containing colloid, altered blood, or watery material; hyalin degeneration; pigment deposit; cholesterol crystal formation; and calcification (Figs. 20 and 21).

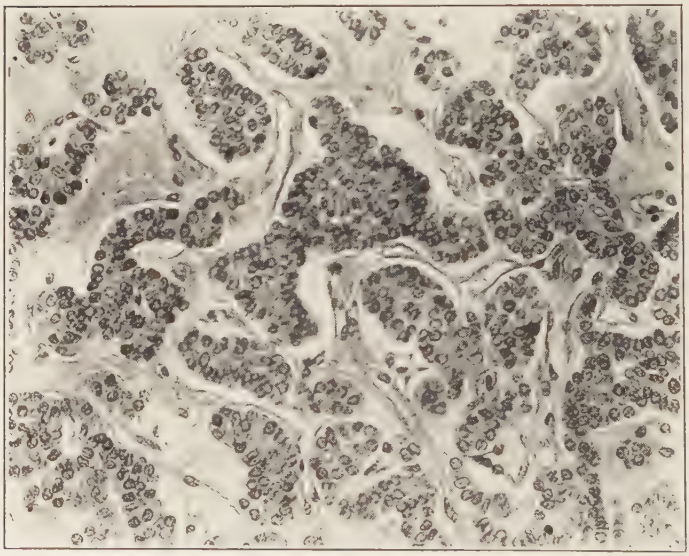

FIG. 19.—Benign fetal adenoma. Note resemblance to embryonic tissue. Immature epithelial cells in curved plates. No vesicles. No colloid. Hyalin stroma.

(*c*) LANGHANS' PROLIFERATING ADENOMA. The tumors of this class are spherical or ovoid, have a definite capsule, and are pale brown and homogeneous on gross section. They may be large. They have a constant structure. The subcapsular tissue is made up of parallel plates of epithelial

cells closely packed together, while the deeper layers show a looser structure, the cells appearing in curled strands, separated by a small quantity of stroma. The interesting points about this type of tumor are its supposed origin from embryonic rests and its proven malignant potentiality.

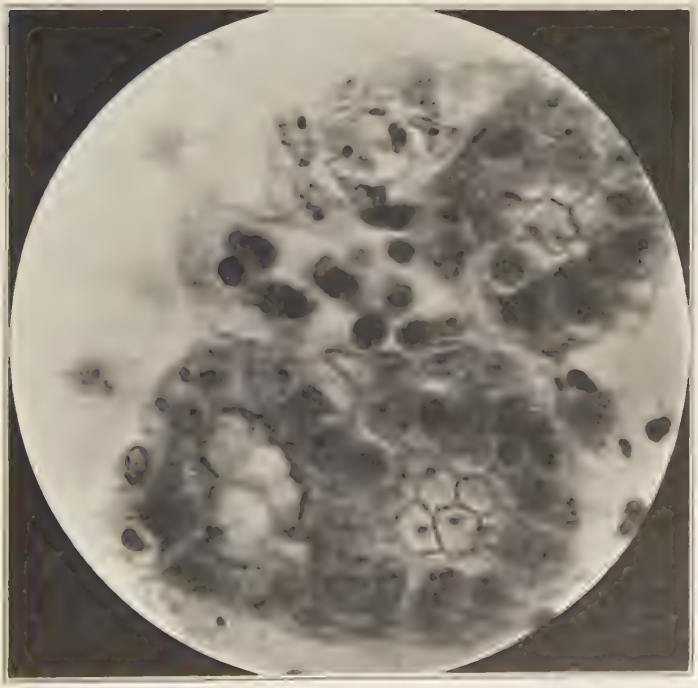

FIG. 20.—Benign adult adenoma, showing small vesicles, blood capillary with erythrocytes and distended microcapillaries.

Parathyroid Adenoma.—Benign or malignant neoplasms may originate in the parathyroid bodies, their structure resembling the normal architecture of these glandules. In the Montreal General Hospital Clinic there was observed one case of large parathyroid adenoma, which presented the

clinical features of benign thyroid tumor. This tumor was encapsulated, and microscopically was made up of columns of closely-packed epithelial cells with palisade arrangement. There was no evidence of malignancy. Microcanaliculi were absent (Fig. 22).

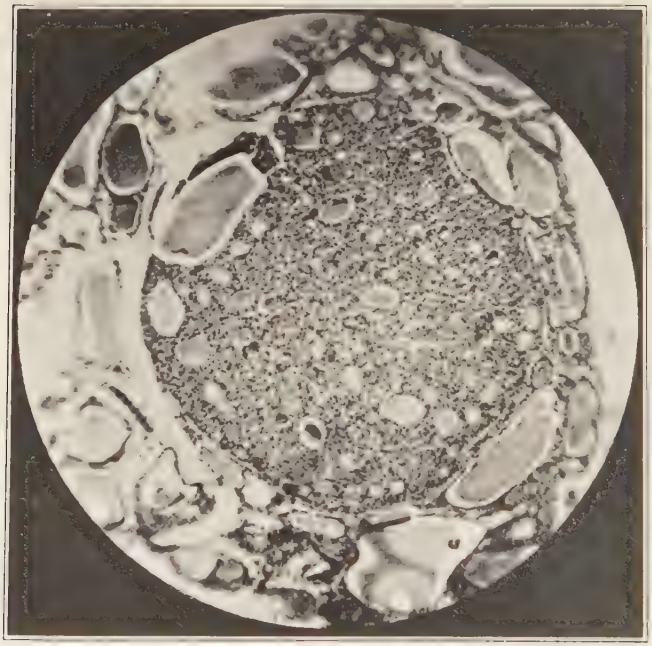

FIG. 21.—Microscopic adult adenoma.

Malignant. Malignant disease develops more commonly in the right lobe of the thyroid gland than in the left, and in the deeper or most posterior parts of the gland. It arises generally in previously existing and apparently benign tumors. In rare instances it develops in a normal gland.

Pathological Diagnosis. Malignant change in an encapsulated adenoma may be extensive before the capsule or the

extracapsular tissues are involved or metastases occur. It is the view of some pathologists, including Simpson, that in certain cases a positive diagnosis cannot be made unless there is, in addition to the ordinary criteria of malignancy, an invasion of the blood capillaries of the capsule.

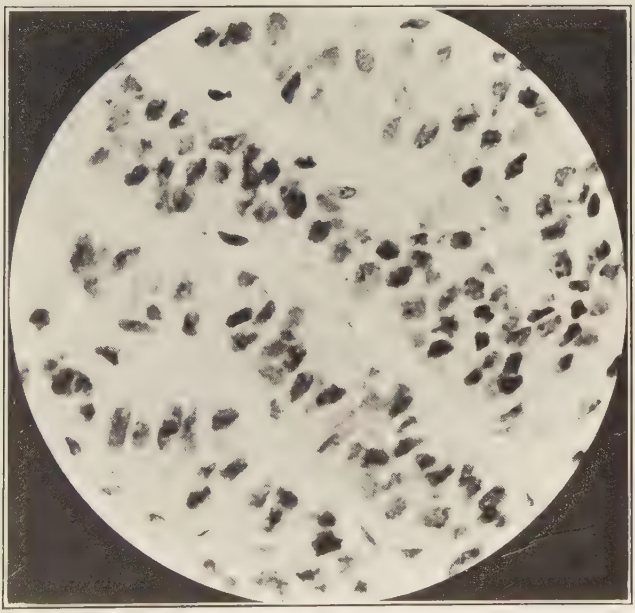

FIG. 22. Benign adenoma of parathyroid body. Epithelial cells in solid columns. (High power.)

Inspection of the gross specimen will often fail to reveal malignant disease, which may nevertheless be present. If, however, the material for microscopic study is carefully selected, a correct decision as to the presence or absence of malignant disease can generally be made. The importance of careful routine study of all thyroid specimens is emphasized by the fact that tumors which have been diagnosed clinically as benign prove occasionally on histological examination to be malignant.

The gross inspection of a thyroid gland in which there is advanced malignant disease reveals the presence of prominent hard nodules, which develop in the deep or posterior parts of the gland and grow in an irregular way. The regional lymphatics are generally invaded before the growth extends through the capsule to the perithyroid tissues. The large bloodvessels may be invaded by tumor growth or they may be occluded by pressure.

The consistence of malignant tumors varies with the type of growth. The cut surface is usually pale and dry, but may be indistinguishable from normal thyroid tissue. The malignant process may be sharply defined from the normal tissue (as in malignant adenoma), or it may be diffuse. Inflammatory changes may be present.

Histologically a malignant thyroid is seldom of uniform structure. In some fields the tissue looks like normal gland, while in others there is deformity of the cells and frequent mitosis.

As a general rule metastases, wherever met with, closely resemble in structure the appearance of normal thyroid tissue. This resemblance is believed to increase with the age of the metastasis, as is the case in benign adenoma.

Metastatic hypernephromas in the thyroid have been reported. The slides from one case in the Montreal General Hospital series presented in many areas the histological features of hypernephroma, but the examination of the sections as a whole justified the diagnosis of primary thyroid cancer. In the illustrations in Wilson's paper on malignant disease of the thyroid there can be seen in certain fields of the sections a close resemblance to Grawitz tumor. Without impugning the work of Klose, Kolodny and others, we think that one should not pronounce a given specimen hypernephroma unless the primary tumor can be demonstrated.

Metastases.—Malignant thyroid tumors spread by contiguity to the tissues of the neck, along the lymphatic channels, or through the blood stream. The method of spread

seems to be related in some way to the histological structure of the original tumor. Carcinoma tends to spread to the cervical tissues immediately adjoining the thyroid. Malignant adenomas generally metastasize to the regional lymph nodes, while a third group of tumors, resembling in histological structure normal thyroid tissue, shows a distinct tendency to invade the blood channels, with the formation of metastases in the lungs and bones.

(*a*) Malignant Adenoma.—*Fetal Type.*—These tumors are composed of encapsulated cellular masses with little or no colloid. The cell structure and arrangement remind one of the fetal thyroid. The subcapsular tissue is well nourished and shows evidence of rapid growth. The tissue in the center of the tumor may show a more mature structure and arrangement, and is subject to degenerative changes. The capsule is ultimately invaded, and metastases develop in the neighboring lymph glands.

Adult Type.—These tumors are large or small nodular growths, which may be present in the thyroid for years without evidence of malignant change. At first they are enclosed by a fibrous connective-tissue capsule, and in structure resemble normal thyroid tissue. When malignancy develops, this resemblance to normal thyroid structure becomes less perfect; the colloid becomes less abundant; and the cells increase in number, become packed together, and show mitosis. The capsule of the nodule and its capillaries are invaded by the advancing growth. Tumor cells penetrate the lymphatics and produce metastases in the cervical lymph glands. Occasionally they penetrate the larger blood channels and are thus widely disseminated. Swelling and pain in metastatic tumors of this type at the menstrual period have been interpreted by von Recklinghausen and others as an indication of functional activity (Figs. 23 and 24).

Papillomatous Type. This lesion consists of incompletely encapsulated masses of soft tissue, into the irregular spaces of which protrude papillomatous growths, consisting of a

delicate arboreal stroma supporting large cuboidal cells. The surrounding thyroid parenchyma is invaded, but lymph-gland metastases are rare. Clinically this is the least malignant type of new growth. Removal may be followed by local recurrence, but repeated operation supplemented by radiation will effect a cure (Fig. 25).

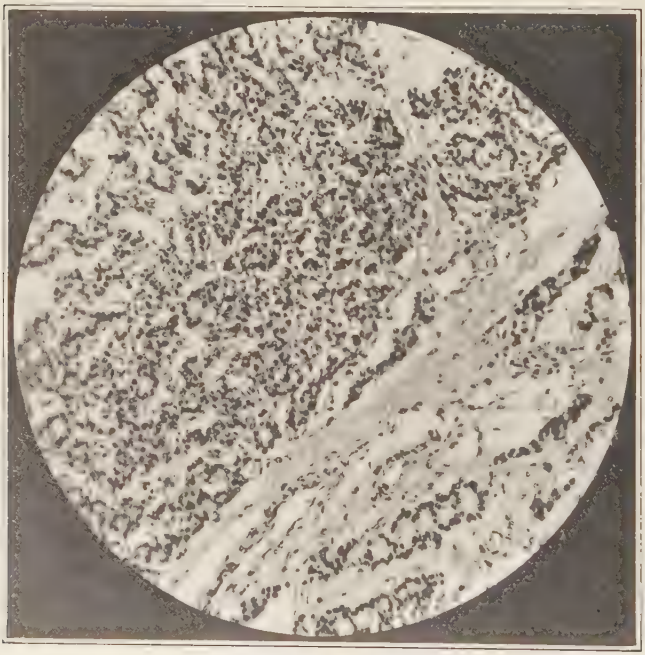

FIG. 23.—Section of malignant adenoma, showing: (1) epithelial cells forming nests and incomplete alveoli, (2) invasion of the capsule.

(*b*) CARCINOMA.—Carcinoma may originate in a nodular goiter or in a normal gland. Three forms are recognized, according to the proportion of fibrous connective tissue present—the simple, the medullary and the scirrhous.

The simple form approximates the normal gland in consistence and gross appearance. The stroma is well developed.

The cells are small and compact. There may be spindle forms. The whole structure may in a general way resemble sarcoma. There is little tendency to alveolar arrangement, the cells forming irregular columns or plates. Karyokinesis is a prominent feature. There is early blood-capillary inva-

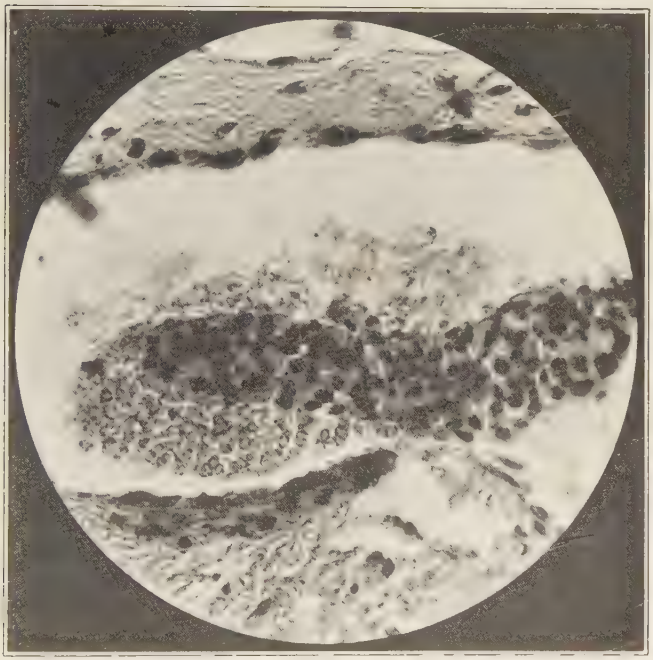

FIG. 24.—Section showing tumor tissue growing in the blood capillaries of the capsule of a malignant adenoma. (High power.)

sion and infiltration of the surrounding tissues. Metastases may resemble the original tumor, but more frequently simulate in structure normal thyroid tissue.

The medullary form is soft, pulpy and hemorrhagic. It shows large epithelial cells without special arrangement, abundant mitoses, and a scanty stroma rich in blood channels.

The scirrhous form is hard, dry, and retracted or scarred. The tumor is not large; in fact the total bulk of the thyroid may be diminished. The course is a chronic one. Histologically the tumor is made up of dense fibrous tissue, in which are embedded islands of epithelial cells. Unless a careful study of the whole tumor is carried out, a mistaken diagnosis of sarcoma may be made.

FIG. 25.—Malignant papilloma of the thyroid gland.

(c) EPITHELIOMA.—Roeder collected 10 cases of epithelioma of the squamous-cell type.

(d) ENDOTHELIOMA. De Quervain has published a careful clinical and pathological study of this lesion under the name of "Struma Maligna Endotheliomatosa." He believes that this tumor always begins as a localized lesion in the thickened wall of an old cyst.

(*e*) Sarcoma.—Sarcoma of the thyroid has been described by many writers including Herbst and Graham. Although Ewing is doubtful whether its existence has been fully established, Zeckwer reports a case of fibrosarcoma, the fibrils of which, she states, were demonstrated histologically

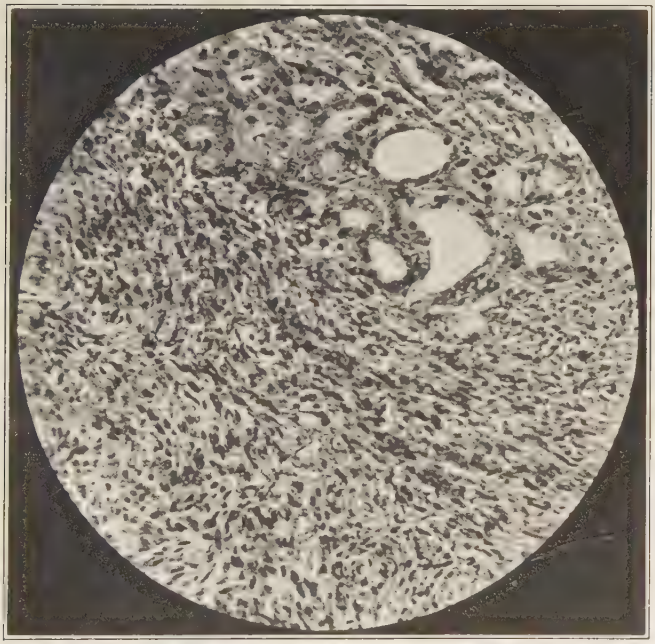

Fig. 26.—Sarcoma of the thyroid gland. The section shows a small group of persisting thyroid vesicles.

by accepted methods of differential staining. A microphotograph of a section from one case met with in the Montreal General Hospital Clinic is here shown (Fig. 26).

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PART II.

CLINICAL.

CHAPTER VI.

CLINICAL CLASSIFICATION.

Since some types of thyroid disease are peculiar to certain countries and the nomenclature of types common to all is not uniform, any clinical classification suggested at the present time must necessarily be more or less local. The nodular goiter described by McCarrison as endemic in the Himalayan foothills, while resembling in many ways the endemic forms seen in Switzerland, is very unlike endemic goiter as we know it in this country. Furthermore, in the Himalayas family or hereditary predisposition to goiter is marked; cretinism, myxedema, deafmutism, and idiocy are met with as sequelæ; and toxicity in nodular goiter is unknown or at all events extremely rare; while in America congenital goiter is an unfamiliar type, cretinism is rare, and thyrotoxicosis in the adenomatous group is extremely common.

The classification which is here presented is based upon personal experience in the province of Quebec, but from observations in other clinics we believe it to be generally applicable to this continent:

Clinical Classification.

Juvenile or Adolescent Goiter *Late Diffuse Colloid Goiter*	Endemic
Graves' Disease (*Exophthalmic Goiter*)	

Combined Graves' and Adenomatous Disease
Iodine Thyrotoxicosis
Adenoma Non-toxic
Adenoma Toxic
Inflammations: I. Thyroiditis
(*a*) Simple (toxic)
(*b*) Ligneous
(*c*) Suppurative
(*d*) Specific
(1) Syphilitic
(2) Actinomycotic
(3) Tuberculous
(*a*) Miliary
(*b*) Caseo-suppurative
(*c*) Lardaceous
(4) Parasitic (Chagas' Disease)
II. Strumitis
(*a*) Simple (toxic)
(*b*) Suppurative
(*c*) Specific
Malignant: I. Malignant Adenoma
(*a*) Fetal
(*b*) Adult
(*c*) Papillomatous
II. Carcinoma
(*a*) Simple
(*b*) Medullary
(*c*) Scirrhous
III. Epithelioma
IV. Endothelioma
V. Sarcoma

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CHAPTER VII.

JUVENILE OR ADOLESCENT GOITER.

Though usually a simple and transient affection, adolescent goiter is of surgical interest for two out-standing reasons: (1) because it occasionally assumes toxic features, with the ultimate development of the Graves' syndrome; and (2) because many patients with adenomatous disease give a history of goiter in adolescence, and it is more than probable that the functional and circulatory disturbances present at that time produced in the gland pathological changes which persisted after the disappearance of the swelling and later, under the stimulus of overwork, pregnancy, or infection, or because of continued iodine shortage, developed into adenomata.

In considering the incidence of thyroid enlargement at adolescence, one must remember that the size of the normal gland is not a fixed quantity. It varies in different localities and may also vary in the same individual in response to special physiological demands. The fact that the gland is palpable or visible on deglutition does not mean that it is goitrous. Many of the so-called "slight enlargements" are physiological and transient. If statistics were based upon strictly pathological enlargements, the recorded incidence of juvenile goiter would undoubtedly be much lower.

Although in some parts of America, northern Michigan for example, adolescent goiter is common in growing boys, in the Province of Quebec the majority of patients are girls, the condition developing immediately before or shortly after the establishment of menstruation. These girls are very often pale, of slack fiber, and lacking in energy.

The swelling is due to colloid storage and involves to a

varying degree both lobes of the thyroid and the isthmus. The consistence is soft. Only rarely is a bruit heard. There are no clinical signs of hyperthyroidism. The basal metabolism is normal or slightly subnormal.

A great deal of important laboratory and clinical research has been directed toward establishing the etiology of this affection, and in reviewing the literature one is impressed with the substance and wealth of the clinical evidence from which the various theories have been deduced. Here, too, one is likely to be unduly influenced by the features which predominate in one's immediate vicinity. It should be borne in mind, however, that what may be considered the prime etiological factor in one country may be of only secondary importance in another. In McCarrison's experience in India the prime factor would appear to be water pollution, whereas on this continent iodine deficiency undoubtedly plays a more important rôle.

Four theories of causation seem to us worthy of comment:

1. The earth-and-water theory, that peculiar geological features render water goitrigenous.

As early as 1680 Wagner drew attention to goiter wells in certain cantons of Switzerland. These waters, it is said, were drunk by young men in the hope of rapidly producing a goiter which would disqualify them for military service. Breitner was consulted by a family in which the parents and seven children had acquired goiters after drinking water from one of these wells. He advised boiling the water, and within four weeks all of the swellings had visibly diminished, only to increase when the family began once more to use unboiled water. Filtration and sedimentation are also believed to lessen the goitrigenous properties of such water.

Some writers think that the goiter is caused by the presence of some particular substance in the water; Grange suggests magnesium; St. Lager, iron and copper pyrites; McClelland, lime. Others think that the harmful effects are due to the absence of some necessary element, such as iodine. Yet, if

iodine deficiency were alone responsible, sterilization or filtration would be without effect.

McCarrison was unable to satisfy himself that there was any close relationship between the endemicity of goiter and certain geological formations.

It is probable that these wells are contaminated, the contamination being destroyed by boiling and materially lessened by filtration and sedimentation. The question of water pollution is considered in the next section.

2. The toxic-infective theory, that goiter is due to a specific flora, the toxins of which affect the thyroid gland.

This is an infinitely more important theory, because water analyses have proved that both goitrous and non-goitrous waters frequently contain equal amounts of iodine. Indeed, instances have been reported where the water used in a goitrous community was particularly rich in iodine. Chatin reports such an instance at Beaulieu in the Department of Oise.

Kocher's advice to boil all water used for domestic purposes suggests a belief in the water-contamination theory, and his statistical reports show that the use of boiled water reduced the incidence of the disease.

Again, the investigations of the Welsh Commission on Goiter led them to the conclusion that the causative factor was in the water, and that it could be abolished by sterilization.

Mottard states that a number of citizens of Bourieux maintained an immunity to goiter in the midst of a goitrous population by the exclusive use of rain water.

More recently McCarrison has recounted the experience of an East Indian community (Sanawar, Punjab), where the substitution of a pure for a contaminated water led to the disappearance of goiter in a population among which the disease had been very prevalent. Furthermore, analyses showed that the imported water was practically free from iodine, and that the iodine content of the local garden earth was low. The conclusion which McCarrison drew from this

alignment of facts was that the determining factor in the development of goiter in this region was "a positive toxic agent derived from the gastro-intestinal tract" and not a deficiency of iodine in the food or water. The rapid decline in the incidence of goiter following the substitution of a pure for a polluted water may, however, have been due to the elimination of bacteria or bacterial products capable of fixing in the intestinal tract the ingested iodine, which, even if scant, would have been sufficient for physiological needs. McCarrison's belief in the value of iodine sufficiency in the prevention, contrasted with his disbelief in iodine insufficiency as a cause of endemic goiter, is illuminating.

3. The theory of iodine deficiency. Before discussing this theory let us recall two important facts: (1) that, under normal conditions, the iodine content of the thyroid gland is higher, per unit of weight, than that of any other body tissue, and (2) that the chief derivative of the thyroid gland, thyroxine, is an iodine compound. From these facts one naturally concludes that a definite quantum of iodine is essential for normal thyroid metabolism and that, if this amount cannot be secured from food and water, derangement of function must necessarily follow.

Substantial proof of the rôle of iodine was first established, experimentally, by the researches of Marine; and later, clinically, by Kimball's work at Akron, Ohio. At the meeting of the American Medical Association in 1928, Kimball reported also the results of exhaustive goiter surveys and water analyses made in the State of Michigan, where goiter is everywhere endemic. In 1924 the Michigan State Department of Health carried out goiter surveys and water analyses in four counties, Houghton, Wexford, Midland and Macomb, these counties being in a line running diagonally from Midland in the northwest to Macomb in the southeast. In Houghton County, where the iodine content of the water was *nil*, the incidence of goiter among the total school population was found to be 58 per cent of the boys and 70.5 per cent of

the girls. In Wexford, where the iodine content of the water was 0.5 parts per billion, the goiter incidence was 47.6 per cent of the boys and 63.4 per cent of the girls. In Midland County, where the iodine content of the water was 7.3 parts per billion, the incidence of goiter was 24.4 per cent of boys and 41 per cent of girls, while in Macomb, where the iodine content of the water was 8.7 parts per billion, the incidence of goiter was 20 per cent among boys and 32 per cent among girls. From this survey it was apparent that the iodine content of the water supply was inversely proportionate to the incidence of goiter. The close interrelationship between iodine shortage and goiter in Michigan was demonstrated further by a survey in 1928 of the city of Midland, where for four years iodized salt had been used continuously in the homes of the public school children. It was found that the incidence of goiter had fallen from 41.6 per cent to 8.8 per cent. Furthermore, to look at the reverse side of the medal, endemic goiter is unknown in the lower Mississippi Valley, where the iodine content of the water is from 10,000 to 18,000 times greater than that of the water of the Lake Superior districts.

Lunde and Nicolaysen of Oslo varied the approach to this question by estimating the amount of iodine excreted in the urine, and found that the amount excreted by adult males in Norwegian school districts was approximately in inverse ratio to the incidence of goiter among adolescents.

In districts where the water is deficient in iodine there is also a scarcity of iodine in the green food. McClendon states that the iodine content of vegetables grown in Minnesota, where 50 per cent of the school girls show thyroid enlargement, is only one-tenth that of vegetables of the same species grown on the New England coast.

Altogether, then, one must conclude not only that iodine is essential to thyroid metabolism, but that a deficiency of iodine may be responsible for the development of the juvenile type of endemic goiter seen on this continent.

4. The theory of multiple causation, involving such factors as diet, overwork, insufficient hours of rest, rapid growth and infection, combined with iodine deficiency or water pollution.

This theory seems to be the most reasonable. A deficiency of iodine in the water supply cannot be the sole cause; otherwise, all of the inhabitants of a goitrous district would have the disease. In the county of Houghton, Michigan, where the iodine content of the water is *nil*, it must be assumed that the 30 per cent of girls and the 42 per cent of boys who escape goiter are able to secure the necessary quantum of iodine from green vegetables or imported foods. Again, while the iodine supply may be sufficient for ordinary needs, it may be insufficient to meet the excessive demands of puberty, rapid growth, or infection. Kimball reports the case of a boy, aged seventeen years, who grew almost a foot in a year, and who, in spite of having taken iodized salt for the three preceding years, developed goiter.

It has frequently been observed that endemic goiter develops more often during the winter, when green vegetables are scarce, than during the summer when they are plentiful. Kendall has quite recently drawn attention to the seasonal variations in the iodine content of the thyroid gland of hogs, the minimum content being recorded in January and the maximum in July and August. Whether these seasonal changes in the iodine content of the gland are due to changes in temperature or to the varying iodine content of the diet has not been determined, but, in his observations upon animals in British Columbia, W. D. Keith found that goiter did not develop when green food was abundant.

In many rural districts the incidence of goiter is said to be on the increase, and for this reason we may with advantage review the question of food supply. In the last generation it was the primary object of the farmer to raise a maintenance crop, which would secure for the family an adequate and varied food supply. His cellars were abundantly stored with

fresh fruits and vegetables for winter use. With the increase in urban population, however, and the widespread introduction of rapid transportation, the outlook of the farmer has undergone a radical change. His efforts are now focussed on the production of a money crop and specialization has largely supplanted general farming. On dairy farms children are frequently deprived of adequate supplies of butter and whole milk. The vegetable garden is abandoned, or relegated to the care of the women and children, and the family not infrequently sits down to a meal of canned food. The growing girl and boy naturally prefer the foods to which they are accustomed, and the taste for fresh green vegetables and fruit, which are the main source of iodine and vitamin supply in interior lands, is not acquired.

The extensive use of canned food in the city may be attributed in part to the general exodus to small apartments, in which there is little room for the storage of vegetables, and to the increasing speed of urban life, which allows little time for the prepartion of meals or their consumption. Canned foods and bought pastry make possible the "quick lunch" habit.

In the primary and secondary schools, too, the curricula have been so expanded that, not only have children insufficient leisure for healthful exercise in the sunshine and open air, but their hours of rest are greatly encroached upon by the heavy assignments of evening study. Frequently they do not finish their preparation until 10 o'clock. This burden of work is imposed during the transition from childhood to adolescence, when developmental processes have reached their greatest acceleration and the functional reserve is being heavily drawn upon. The broad disparity between the incidence of the disease in boys and girls is apparently attributable to the added strain thrown upon the thyroid gland by the establishment of menstruation.

Again, within recent years indoor gymnastics have been made compulsory. One of the primary objects of regulated physical exercise is to improve oxygenation of the tissues,

but, where physical drill is performed within four walls, in an atmosphere which is necessarily vitiated, and where a chance sunbeam discloses to the observer columns of dancing motes, this object is frustrated. The idea of physical drill during study hours was introduced by the Swiss, but in Switzerland the children march into the open air for calisthenics.

In addition to the increase in school activities, the amusements of modern life—the automobile, the radio, the movies, organized athletics, dancing—all postpone the bedtime hour and, as a consequence, young people today generally get insufficient rest in bed, at a time in life when such rest is most essential. There is, too, among the younger generation a gradually increasing disregard of discipline. Less and less heed is paid to parental counsel, and it would seem that less and less parental counsel is given. For a tranquil home life there is substituted a feverish unrest, with a constant drain upon the physical resources.

PROPHYLAXIS IN JUVENILE OR ADOLESCENT GOITER.

The prevention of juvenile goiter would seem to depend not only on a sufficiency of iodine in food and water and the elimination of bacteria from these commodities, but also on the control of the energy output and the maintenance of a physical reserve adequate for the needs of the period of growth and development. And its prevention is of the utmost importance, because, once abnormal circulatory activity or deranged secretory function has been established in the thyroid gland, it may not be possible, even under the most favorable conditions, to secure a return to normal. Furthermore, in eliminating the conditions under which juvenile goiter develops, one would not only lessen the incidence of Graves' disease (also an affection in which iodine shortage and physical strain are contributing factors), but also forestall those cases of adenomatous disease which have their

beginnings in the circulatory and functional derangement of the gland at puberty.

Preventive measures naturally differ in different localities. In districts where the iodine content of the food and water is adequate and where adolescent goiter is met with only sporadically, emphasis should be laid upon a rational mode of life and the inclusion in the diet of iodine-and-vitamin-containing foods. In goitrous districts, where the iodine content of the food and water is low, prophylactic doses of iodine must be given as well. The work of Kimball may be quoted again to illustrate the efficacy of this measure. Of 2190 school girls living in the goitrous district of Akron, Ohio, who showed no signs of thyroid enlargement, but who were given small doses of sodium iodide in two courses during a period of twelve months (the total amount administered being in each case 2 gm.), only 5 developed enlargement of the thyroid during the year, while in a control series of 2305 children, to whom prophylactic treatment was not administered, 495 developed thyroid enlargement.

In this province, as in the American states bordering on the Great Lakes, it is the practice of the medical supervisors of public schools to recommend that all girl pupils over ten years of age should take each week of the forty weeks of the school year one chocolate tablet of Iodostarine-Roche. These tablets contain 10 mg. of iodine in organic combination. The State Health Department of Michigan, in promoting the manufacture and advising the use of iodized salt, recommended a standard of 1 part of potassium iodide to 5000 parts of salt. On the basis of an annual per caput consumption of $7\frac{1}{2}$ pounds, the dosage is 10 grains of potassium iodide or 400 mg. of iodine, the same as that contained in 40 chocolate tablets. The standard recommended by the Swiss Goiter Commission in 1922 is 1 part of potassium iodide to 200,000 parts of salt, or a yearly dosage of only 15 or 20 mg. of iodine.

It is Kimball's opinion that there has never been a case of hyperthyroidism in a child which could be attributed to the

prophylactic administration of iodine in amounts sufficient to prevent goiter. On the other hand Bircher in 1925, in reviewing the results of the introduction in 1922 of iodized salt in certain cantons of Switzerland, states that, apart from a very marked increase in the incidence of Graves' disease, a very large increase in the number of cases of iodine thyrotoxicosis had been observed, the increase being most marked in those cantons in which the propaganda for iodine therapy had been most active.

TREATMENT OF JUVENILE OR ADOLESCENT GOITER.

In the treatment of juvenile goiter the administration of iodine has become a universal practice. The results recorded by Kimball in his work at Akron, Ohio, and by Klinger in Switzerland, are most convincing. Of 1182 school girls with adolescent goiter, treated by Kimball with sodium iodide, a decrease in the size of the gland was noted in 773, while in a control series of 1048 untreated cases a decrease was noted in but 145. Klinger reports that of 684 children treated for fifteen months with from 10 to 15 mg. of iodide weekly, only 191 remained goitrous. While these figures prove convincingly the value of iodine as a therapeutic agent, there still remains for the period treated a very appreciable percentage of uncured cases, a percentage which is thrown into sharp relief when compared with the small percentage of patients who developed goiter while taking prophylactic doses of iodine.

When thyroid extract is given before or with the iodine, the gland recedes more rapidly than when iodine alone is used. In the Montreal General Hospital Goiter Clinic the routine practice is to give to patients of normal weight, between the ages of fourteen and sixteen years, 1 grain of thyroid extract (whole gland) daily before breakfast for one week. If at the end of this time there is no increase in the pulse-rate and no loss of weight, the course is repeated. Either with or follow-

ing the course of thyroid extract, iodine in the form of Lugol's solution (compound iodine solution—iodine, 20 grains; potassium iodide, 30 grains; distilled water to 1 ounce; available iodine per minim 5.27 mg.), 1 minim daily in alternate months, is prescribed. Younger children are given smaller dosages. By prescribing Lugol's solution diluted 1 to 1 or 1 to 2 with distilled water, one can reduce the dosage to one-half or one-third. The dilution should not be left to the patient. In most instances the use of iodine is remitted during the summer months, when green food is more abundant, and in all instances where the summer vacation is spent at the seaside. Assuming that no iodine is taken during the four summer months, the amount taken during four of the remaining months, that is in alternate months, is for the dosages of 1 minim, $\frac{1}{2}$ minim and $\frac{1}{3}$ minim of Lugol's solution, 634 mg., 317 mg., and 211 mg. respectively.

Cod-liver oil, because of its high iodine and vitamin content, should also be prescribed during the winter months.

Each patient is given a printed form covering hours of rest, diet, and exercise. The regulation of the diet ensures a normal iodine supply irrespective of medication, and has the added advantage of training the patient to like the foodstuffs which are essential for the maintenance of normal health in a goitrous region such as the Province of Quebec.

Constipation should be combated by careful regulation of the diet and the cultivation of a regular hour for going to stool.

If there is reason to suppose that the water supply is polluted, boiled or filtered water should be used and intestinal antiseptics such as salol, thymol, or beta naphthol, should be prescribed. Bacillus bulgaricus also is said to be effective in abolishing a toxic intestinal flora (McCarrison).

If there is any suggestion of increased or diminished thyroid function, basal metabolic determinations should be made.

The most exaggerated form of adolescent goiter is met with

in young men. Occasionally the swelling is so great that tracheal compression and stridor develop (Fig. 27).

For the relief of pressure symptoms absolute rest in bed for at least one month and the administration of thyroid extract and iodine are essential. Subsequently the diet and hours of work and rest must be strictly regulated.

FIG. 27.—Exaggerated form of adolescent goiter with respiratory stridor, in boy aged eighteen years.

It should be borne in mind that colloid goiters vary in their pathological anatomy. In one type, fortunately by far the commoner, hypertrophy of the epithelial elements keeps pace with the colloid storage, and the normal relation between the two physiological phases is maintained. In the other, comparatively rare type, the secretory phase is diminished or suppressed, resulting in hypothyroidism, ranging from a

slightly but constantly subnormal rate to the status of definite myxedema. A case of this kind was seen in the Goiter Clinic (Fig. 28). The patient, a girl aged fifteen years, had gross enlargement of the thyroid with secretory insufficiency and myxedema. The basal metabolic rate was −30. She was referred to the medical department for observation and treatment. The photograph of this patient

FIG. 28.—Colloid goiter with myxedema.

depicts the characteristic aspect of patients with so-called "goiter with myxedema."

The question is frequently asked, how long should iodine treatment be continued? If at the end of two years there is no palpable evidence of enlargement and the patient has acquired satisfactory habits with respect to diet and hours of rest, iodine treatment may safely be discontinued. But,

if the enlargement tends to persist, although lessened in size, iodine treatment should be continued indefinitely, in minimal amounts with periods of remission, and always under medical supervision. Long-standing cases are less amenable to treatment than are recent cases.

Women who have had adolescent goiter should be given iodine throughout subsequent pregnancies and periods of lactation.

INSTRUCTION SHEET.

Date_____

Instructions for _____

Diet: A liberal diet including a fresh green vegetable daily (cabbage, spinach, lettuce, celery, peas, beans, cauliflower, etc.), fresh fruits, whole milk, butter, cheese, eggs, nuts, chocolate, cocoa, whole wheat bread.

Sea food three times a week—oysters, lobster, salmon, haddock, halibut, mackerel, cod, etc. Fish should be baked or broiled, *but not boiled.* If fresh sea fish is not available, use the salt varieties such as salt or kippered herring, finnan-haddie, cod, etc. or freshly-canned salmon.

Rest: Rest in bed_____hours a night, from_____P.M. to_____A.M.

Rest in the afternoon_____hours.

Exercise: No gymnasium, swift games, dancing or swimming.

Walking in the open air, avoiding hills,_____ minutes, morning and afternoon.

Medicine: As prescribed. Do not take more or have the prescription renewed without instruction.

To report again in_____

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CHAPTER VIII.

LATE COLLOID GOITER.

While colloid goiter is more common in adolescence, it is not infrequently met with in persons between the ages of eighteen and thirty years. We have had several cases in school teachers, who are under unusual strain.

In these late colloid cases the thyroid is sometimes distinctly lobulated, as in adenomatous disease. The lobulations, however, are not globular as are adenomatous tumors. Symptoms of nervousness, irritability, and fatigue may be present. The basal metabolism, while within normal limits, tends toward the subnormal.

These patients should not be subjected to operation. Small doses of thyroid extract and iodine, proper hours of rest, daily walking exercise in the open air, and a suitable diet, along the lines of that prescribed for the adolescent cases, are usually effectual, resulting within one and a half to two years in a marked diminution in the size of the gland and a change in its consistence from firm to soft.

CHAPTER IX.

GRAVES' DISEASE.

While Graves' disease or exophthalmic goiter may develop as a transition from juvenile goiter, it is generally a separate and distinct entity.

It is met with in much the same geographical zones as is the goiter of puberty and is probably also, in part, an iodine-shortage disease. Lunde found very small quantities of iodine in the glands of patients suffering from exophthalmic goiter.

There appears to be a predisposition to the disease in certain families, and the disease is likely to be of the same type in members of the same family. This familial group may ultimately be found to embrace chiefly those who have inherited an autonomic instability. (See Case Report No. 1.)

Of proximate factors which determine the time of onset and the severity of the dysthyroidism, the most outstanding are pregnancy, miscarriage, lactation, influenza, focal infections (especially tonsillitis and quinsy), physical and mental strain, and mental shock.

In a series of 334 patients treated surgically to a conclusion in the Montreal General Hospital Goiter Clinic, there were 30 (9 per cent) in whom symptoms developed during pregnancy or lactation. In 26 cases (8 per cent) symptoms developed during or shortly after convalescence from influenza. That influenza should be an exciting cause is not surprising, in view of its well-known depressant effect upon the general physical status. In 18 instances the initial symptoms developed immediately after an acute attack of tonsillitis or quinsy. In a much larger number of cases, of the chronic type, an exacerbation or recurrence of symptoms followed upon ton-

sillar infection. In still other cases tonsillar infection, though not definitely assigned as the primary exciting cause, was probably an added factor. This is suggested by the fact that 140 of the 334 patients (42 per cent) were found on routine examination to have diseased tonsils. In 80 cases (24 per cent) dental infection was present.

Of those who suffer from physical strain, the housewife who, unassisted, does her own housework and is solely responsible for the care of her children is an outstanding example. Few of these women get sufficient rest or know a day's respite from duty. Of the 152 housewives in this series many were drudges, overwhelmed with work and oppressed with family cares.

Mental shock, such as an escape from fire or drowning, an encounter with burglars, a sudden death in the family, immediately preceded the onset of symptoms in 13 cases (4 per cent). Fifty-five of our patients (16.4 per cent) were found to be engaged in occupations involving mental strain. In this group were stenographers, school teachers, nurses, telephone operators, locomotive engineers and attendants on insane patients.

The age incidence lies chiefly within the third and fourth decades, but the disease may occur in infancy and childhood and is not uncommon in persons over forty years of age.

Figures cited by different writers show a wide variation in the sex ratio. There can be no doubt, however, that the disease is much commoner in females than in males. In the Montreal General Hospital series there were 277 females and 57 males, a ratio of about 5 to 1.

The clinical phenomena of Graves' disease are, it is thought, not due to a pure hyperthyroidism, that is an excessive secretion of the normal physiological product, but rather to the elaboration in excessive amounts of a qualitatively abnormal hormone.

There are several clinical types of Graves' disease. Since the determination of the patient's metabolism has become a

routine hospital practice, increasing numbers of the larval forms have been recognized. The presence of tachycardia and tremor, with or without enlargement of the thyroid gland, was formerly not considered very conclusive evidence of Graves' disease, but the demonstration of a persistently elevated basal metabolism in combination with these symptoms renders the diagnosis of thyroid dysfunction comparatively easy, and it is of the utmost importance that these mild forms should be recognized and treated. With few exceptions they yield promptly to rest and iodine therapy, whereas, if overlooked, they are apt to grow worse and to exhibit within a short time the full Graves' syndrome, especially if influenza, tonsillar infection, or pregnancy should supervene, or the patient be subjected to undue physical strain.

One should here mention in parenthesis those cases of thyroid enlargement associated with nervousness, tremor, moderate tachycardia, and incapacity for sustained effort, in which, however, the basal metabolic rate is persistently normal or slightly subnormal. Whether these cases should be included in the class of incipient or larval Graves' disease is a moot question. With the administration of Lugol's solution in small doses the thyroid diminishes in size and becomes softer. One's impression is that the underlying cause of the symptoms is an unstable autonomic system. If this view should be substantiated, it will account for the chronicity of the symptoms. These patients are of the esthetic type, have never had a robust appetite, are usually poorly nourished, and, were it not for the enlargement of the thyroid gland, would be looked upon as psychasthenics.

Next to the larval form, in order of importance from the standpoint of early recognition and immediate treatment, is the fulminating type, in which the patient suddenly becomes acutely ill, with excessive tachycardia, vomiting, diarrhea, and mental irritability. Frequently there is delirium, sometimes delusions or hallucinations, more rarely acute mania.

The tremor of the hand may not be evident at this stage and there may be no obvious enlargement of the thyroid. Ocular signs are usually absent. If the condition is not recognized and iodine is not promptly administered, a rapidly fatal termination may ensue. The following case report exemplifies this type.

Case Report No. 1.

Female, aged nineteen years. Schoolgirl. Seen in her home September 12, 1923.

Family History: Mother emotional and nervous; asthmatic. In 1921 brother, aged twelve years, died of acute Graves' disease.

Past History: Emotional temperament. Led school in gymnasium work. During summer of 1923 had a love affair, which ended abruptly.

Present Illness: Sudden onset September 6, 1923, with nausea, vomiting, diarrhea, rapid pulse, and delirium at times. The menstrual period due at this time was suppressed.

Present Condition: Patient well nourished, although losing weight rapidly. Face and neck suffused. Expression anxious, with slight stare. Widening of palpebral fissure and lagging of upper lid. Speech incoherent at times. Slight tremor of hands. Restlessness and irritability. Dyspnea, with cyanosis of finger nails. Moderate grade of generalized enlargement of thyroid; visible pulsation, but no thrill or bruit; consistence soft. Transverse cardiac dulness, 9 cm.; pulse, 130, regular, volume variable; blood pressure, 126/60.

Diagnosis: Graves' disease of fulminating type.

Treatment: Lugol's solution; bromides; absolute rest in bed; isolation. Because of patient's critical condition, the basal metabolic rate could not be determined.

Severe circulatory crises developed at about 5 P.M. on September 12, 13 and 14, the pulse rising to 170. On each occasion it was thought that death was imminent. Subsequently there was a gradual improvement, with gain in weight. On January 2, 1924, patient removed to hospital. January 3, basal metabolic rate, +56; weight, 108. January

10, basal metabolic rate, +33; weight, 110. January 17 basal metabolic rate, +31; weight, 113.

Operation January 21: Under gas oxygen and later open ether, and local infiltration with novocain, right lobectomy, with removal of isthmus.

February 1: Basal metabolic rate, +20. February 4 returned to home. March 10 readmitted. There was a marked improvement in general condition. Basal metabolic rate, +44.

Operation March 17: Under open ether, left lobectomy. March 24, basal metabolic rate, +10. The subsequent course of the case was uneventful. For the past three years the patient has been energetically engaged in building up a private business enterprise. The basal metabolism and pulse rate have been constantly normal.

Still another type is that in which the cardiovascular phenomena dominate the picture. The symptoms of nervousness, tremor, excitability, cutaneous flushing, and moderate increase in heat production, are all present, but are completely overshadowed by the excessive rapidity of the heart rate, which may range from 160 to 200, or even higher. There is no delirium. The patient's expression is comparatively tranquil. The nutrition is unimpaired. Circulatory crises may occur daily. In one of these the patient may die. In the conduct of these cases time would appear to be the most important factor. Iodine is comparatively ineffective, but should be given in doses proportionate to the basal metabolic rate. Triple bromides in 30-grain doses should be given every twelve hours, or as an alternative Luminal, 1½ grains. Ice-packs and the application of ice-bags to the precordium and neck are also important aids. Everything which may stimulate afferent impulses, including ocular and aural, should be eliminated, because these are quickly reflected in the heart rate. Strict isolation in a darkened room is essential. The patient should be fed by the nurse. If cardiac dilatation and edema develop, digitalis is indicated.

Any attempt at surgical interference while the cardiac crises persist is certain to end fatally. When there is definite improvement in the pulse rate, successive ligations of the upper poles should be undertaken. Later, subtotal thyroidectomy in one or two stages should be performed. As illustrative of this type of thyroid intoxication the following case reports are given in detail:

Case Report No. 2.

Female, aged fifteen years, seen in consultation on November 27, 1925. I am indebted to a colleague for the following notes:

Present Illness: In 1923, at age of thirteen years, the patient (always very athletic) first noticed nervousness, which gradually became worse. She continued her games and swimming, however. In August, 1925, enlargement of neck first noticed. The physician consulted in September prescribed thyroid extract, 1 grain t.i.d., which was taken for three weeks. On October 19 the patient was admitted to one of the city hospitals.

Condition on Admission: Well nourished. Prominent uniform enlargement of thyroid gland. Visible pulsation and loud bruit. No eye signs. Tremor of hand. Expression tranquil. Heart, apex beat in fifth i.s., 12 cm. to left of midsternal line.

October 21: Basal metabolic rate, +33; pulse, 144. October 24, basal metabolic rate, +23; pulse, 128. No medication in interval. Returned home to rest in bed with ice-bag to heart. On November 10 Lugol's solution 2 ♏ daily prescribed.

November 16: Readmitted to hospital. Pulse rate during period at home remained unchanged. November 17, basal metabolic rate, +13; pulse, 128. On November 18 Lugol's increased to 2 ♏ b.i.d. and on November 19, to 5 ♏ b.i.d. The pulse rate continued to increase gradually. On November 23 Lugol's discontinued and patient given tincture digitalis, 10 ♏ t.i.d. November 24, basal metabolic rate, +34; pulse, 150. November 27, Lugol's renewed, 5 ♏ b.i.d.

November 30, basal metabolic rate, +25; pulse, 172. On December 1 and again on December 2 patient taken to operating room in order to familiarize her with surroundings.

Operation: December 3, under gas anesthesia. Whole of right lobe and three-quarters of left lobe removed. Time, thirty-five minutes. Following operation pulse, 160.

Postoperative Course: On December 4 pulse range 180 to above 200. Temperature, 103° F. Nervousness and restlessness not marked features. Died December 5 from what appeared to be circulatory failure.

Pathological Diagnosis: Graves' disease.

Case Report No. 3.

Female, aged nineteen years. Typist. Seen at clinic December 29, 1926.

Complaints: Enlargement of neck, palpitation, nervousness, headache.

Family History: Sister with juvenile goiter attending clinic.

Present Illness: Enlargement of neck at twelve years of age; disappeared in three months under iodine treatment. In June, 1926, enlargement again noticed, with nervousness and palpitation. Took Lugol's solution, 5 ♏ b.i.d., for two months, with relief of symptoms and gain in weight, although working eight hours daily. Tonsillectomy in November, 1926, after tonsillitis. Iodine, 2 ♏ daily, begun again on December 1.

Examination: Tired expression. Mental state tranquil. Temperature, 99.2° F. Weight, 108½ pounds. One lower molar carious. Skin moist. Flushing of face and neck. Tremor of hands, lips, and tongue. Nervous; restless. Moderate grade of symmetrical enlargement of thyroid; consistence firm; pulsation, thrill and bruit. No ocular signs. T. C. D., 14 cm. Loud systolic murmur over whole precordium. Pulse, 164, regular, good volume. Blood pressure, 136/56. Edema of ankles. Lugol's, 2 ♏ daily, and bed rest prescribed.

January 7, 1927: Admitted to medical service of Dr. C. P. Howard. Cardiogram: accentuated *T* wave; no diastole; tachycardia. Pulse very rapid under examination. Severe left frontal headache at times. Fundi normal. Urine normal. Laryngoscopic: inferior poles of tonsils present; vocal cords normal. Postnasal discharge. Roentgen-rays: thoracic organs normal; no cloudiness in any of the accessory nasal sinuses; skull (stereoscopic), pituitary fossa normal.

Diagnosis: Graves' disease.

Treatment: Absolute rest in screened bed; Lugol's solution, 7 ♏ t.i.d. One visitor for ten minutes three times a week.

On February 2 basal metabolic rate, +13; but pulse constantly between 110 and 120. On February 10 an attack of acute sore throat. Patient depressed, and complained of palpitation. Attack subsided in five days. On February 25 basal metabolic rate, +32. Weight maintained, but no improvement in general condition. Lugol's discontinued. After iodine stopped, general condition became worse. Palpitation became severe and constant; and weakness, irritability, and headache developed. Complained constantly. Very restless, and irregularity in pulse noted for first time. On March 1 basal metabolic rate, +28. Lugol's renewed, 20 ♏ t.i.d. On March 5 basal metabolic rate, +33. After iodine renewed, general condition improved very much. Symptoms subsided and irregularity of pulse disappeared. On March 10 basal metabolic rate, +24; pulse, 134; weight, 102 pounds.

Operation: March 16, under local anesthesia, bilateral polar ligation. Reaction severe. Temperature, 100.8° F.; pulse, 160; vomiting. March 27, pulse below 100 for first time. Tranquil mentally. April 2, basal metabolic rate, −1, pulse, 84. April 13, basal metabolic rate, +13; weight, 102; pulse, 84. Discharged. To rest in bed and take Lugol's solution, 5 ♏ t.i.d.

May 25: Readmitted. Basal metabolic rate, +49 (illustrating fleeting effect of ligation); pulse, 132; weight, 105. General condition the same as when discharged. Following ligation had roentgen-ray treatments (3) at intervals of

three weeks. June 3, basal metabolic rate, +30; June 7, +30; June 11, +39. Pulse regular, 110 to 130, always rapid except when taken by nurse.

Operation: June 14, under local anesthesia, subtotal thyroidectomy. Some adhesions as result of roentgen-ray treatments. Gland moderately enlarged, very friable. Pathological diagnosis, adenoid goiter (Graves' disease) with involution.

Postoperative Course: Moderate febrile reaction. Pulse maximum, 160. Not restless. June 24, basal metabolic rate, +5; weight, 103; pulse, 78 to 90. Discharged July 9.

Record for following year uneventful, basal metabolic rate ranging between, +7 and −12. Weight, 130. Pulse range 64 to 78. No symptoms. Took iodine in diminishing doses until February, 1928.

By far the commonest type of Graves' disease, however, is that which, without being recognized, develops fully within a period of from three to six months, and eventually becomes chronic, periods of activity alternating with periods of comparative quiescence. The first symptoms are tachycardia, tremor, weakness, loss of weight, sweating, restlessness, increased appetite and sometimes vomiting and diarrhea. Enlargement of the gland usually becomes noticeable within three months of the onset of symptoms, but sometimes it precedes them by weeks or months. It is of varying size. Occasionally there is no enlargement whatever, though the symptoms of intoxication may be of the severest type. Definite ocular signs, such as widening of the palpebral aperture (Stellwag's sign), lagging of the upper lid (Graefe's sign), stare, and lack of convergence (Moebius' sign), make their appearance within three months of the onset of symptoms. Flattening of the forehead (Joffroy's sign) is generally present also. True exophthalmos does not usually develop until later.

If at this stage rest be enforced and iodine administered, the return to a normal standard of weight and a feeling of well-

being is frequently rapid, but there remain as a rule certain objective symptoms, namely, moderate acceleration of the pulse rate, tremor of the hand especially on excitement, and a basal rate which is constantly above normal (+10 to +20).

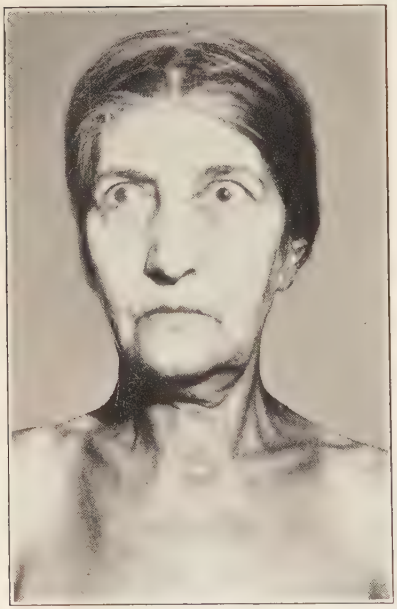

Fig. 29

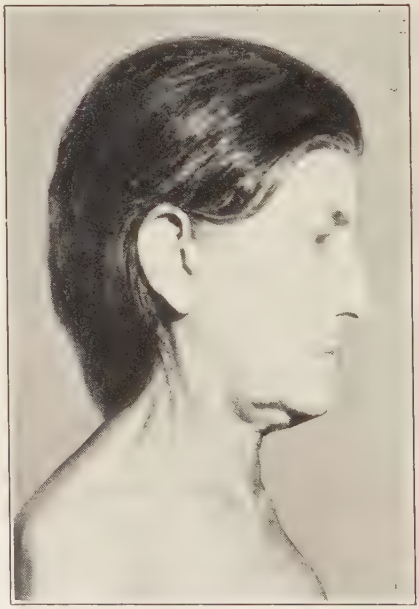

Fig. 30

Figs. 29 and 30.—Marked eye signs, *i. e.*, widening of palpebral aperture, lagging of upper lid, pronounced stare. The front view (Fig. 29) also suggests definite exophthalmos which, however, is shown by the side view (Fig. 30) not to be present.

With the recurrence of infection or other exciting cause the cycle is renewed, with ever increasing severity. Other symptoms manifest themselves. Restlessness may be so severe as to lead to excoriation of the knees and elbows and, if unrelieved, is a serious omen. Occasionally patients are extremely emotional and subject to crying spells. Mental irritability is a variable symptom, in many cases taking the

form of an unreasonableness which keeps such patients constantly at odds with their environment. The expression is usually alert and anxious, the corneæ glistening. The face is in some cases flushed, due to capillary dilatation; in others, pale. The pale subjects as a rule are unfavorable operative risks. Sometimes there is a fugitive erythema about the neck and upper part of the chest. Dermographism is pronounced. The skin is moist. Sweats are frequent. The temperature is usually slightly elevated, ranging from normal to 99.4° F. The appetite is increased, often voracious. Diarrhea and vomiting occur in many of the severely toxic cases. Occasionally there is abdominal pain. Tremor may involve not only the hands, but the lips and tongue as well; in aggravated cases, the whole body. Palpitation is a very constant complaint. Precordial thumping, especially when the patient is lying down, may be a distressing symptom. Insomnia is not uncommon. Headaches occur occasionally and may be severe. Heat intolerance is always present if the basal metabolism is high. If the patient keeps going about, edema of the ankles develops. The loss of weight may be rapid. While muscular weakness is general, it is noted especially in the quadriceps extensor, the internal rectus muscles of the eye, and the anterior belly of the occipito-frontalis. The quadriceps weakness is evident when the patient attempts to step up or to hold the leg in extension while sitting. The selective action of the toxin upon the anterior belly of the occipito-frontalis is seen in inability to wrinkle the forehead, a flattened, expressionless forehead being a very characteristic sign. The same toxic degeneration affects the internal rectus muscle of the eye, causing loss of power of convergence. In rare cases all of the oculo-motor muscles are involved, as in the case here briefly cited.

Case Report No. 4.

Female, aged thirty years, unmarried. Domestic. Admitted December 23, 1927.

Present Illness: Following severe "cold" seven weeks ago noticed drooping of left upper eyelid, and one week later enlargement of thyroid gland.

Examination: Full Graves' syndrome. Basal metabolic rate, +67.

Report by Dr. Gilhooly on Eyes: Marked bilateral ptosis. Wrinkling of forehead absent. Infrequent winking. Widening of palpebral fissure. Lagging of upper lid. Exophthalmos, more marked in left eye. Movements of eyeballs restricted in all directions, but there is not complete immobility. Movements of elevators and depressors more restricted than those of lateral muscles. Pupils react to light and accommodation. No blurring of vision.

Treatment: Rest in bed, Lugol's solution, 5 ♏ b.i.d. January 26, 1928, basal metabolic rate, +27; weight, 115. Subtotal thyroidectomy under local anesthesia. Uneventful recovery. Discharged February 10; basal metabolic rate, −9.

Report by Dr. Gilhooly April 18, 1928: Patient feels that her eyes move more than they did. Undoubtedly movement has increased in the six cardinal directions. Improvement most marked in lateral movements. Still has quite marked ptosis. Exophthalmos less.

October 17: Basal metabolic rate, +3; weight, 130½. Since June has been working as cook. No complaints. No tremor; pulse, 76.

November 3, 1928: Examined by Dr. Hanford McKee, who reports that the former complete paralysis of extrinsic muscles has improved, so that now there is perceptible movement in all directions, though the action of the left external rectus is just perceptible. Both eyes react to light and accommodation.

Comment: The persistence of paralysis in this case supports our statement that the effects of thyrotoxicosis may endure long after operation and the restoration of metabolism to normal.

Tumors other than those of the thyroid may produce eye signs. A case of this kind was met with in the clinic. So striking was the appearance of this man on entering the clinic

that he was at first glance thought to be a case of Graves' disease (Fig. 31).

The tumor in the neck was large, occupying the median line. The surface was smooth. The pulse was found to be normal; there was no tremor of the hand; and the basal metabolism confirmed the clinical evidence of normal thyroid function.

FIG. 31.—Median line dermoid cyst. Note marked widening of palpebral fissure. Lagging of upper lid was also present. There was no tremor, tachycardia or elevation of the basal metabolism. Eye signs disappeared within three months after operation.

The tumor proved to be a congenital dermoid cyst, compressing both upper poles of the thyroid, especially the right, and causing right-sided deformity of the lower margin of the thyroid cartilage. The photograph illustrates the typical stare of the thyrotoxic patient. The removal of the tumor was followed by a gradual disappearance of the ocular signs.

Pigmentation of the eyelids is an unusual sign. Most striking is an edema of the eyelids seen only in very toxic cases.

With the general failure of nutrition there is frequently marked falling of the hair, and occasionally atrophic changes in the finger nails.

The enlargement of the thyroid is generally uniform, although the left lobe, because of its deeper position, usually appears to be smaller than the right. The surface is sometimes smooth, sometimes granular. On deglutition mobility is normal. As the disease progresses the consistence gradually changes from soft to hard. The gland is not tender. Pulsation is generally visible, a thrill is frequently palpable, and a bruit can almost always be heard over the whole gland or at all events over the superior thyroid vessels. The intensity of the pulsation and bruit lessens under rest and iodine medication. The proximal lymph nodes are not enlarged. There is no compression or displacement of the trachea. The voice is seldom affected. The pulse rate varies from 100 to 140; commonly it is 120. It is regular, except in those cases of long standing in which fibrillation has developed. The volume is good. In well-established cases there is always an increase in the transverse cardiac dulness, due generally to dilatation. Of heart murmurs the most common is a basal systolic, heard frequently at the apex, but not transmitted to the axilla. The systolic pressure is, as a rule, normal, except in periods of excitement with sudden acceleration of the pulse rate, when it may be considerably raised. There is usually an increase in the pulse pressure.

Myocardial changes may develop during a period of exacerbation, but it is astonishing how long tachycardia may persist, especially in younger subjects, without evidence of myocardial damage. Furthermore, it has been our experience in cases of Graves' disease in which auricular fibrillation has supervened that the rhythm generally becomes normal again after thyroidectomy, in contrast to the persistence of

fibrillation in cases of toxic adenoma after enucleation resection.

The development of fibrillation from lack of radical treatment (the patient having first of all refused operation and later, after ligation, having postponed the major operation) and the restoration of normal rhythm after thyroidectomy are illustrated by the following report:

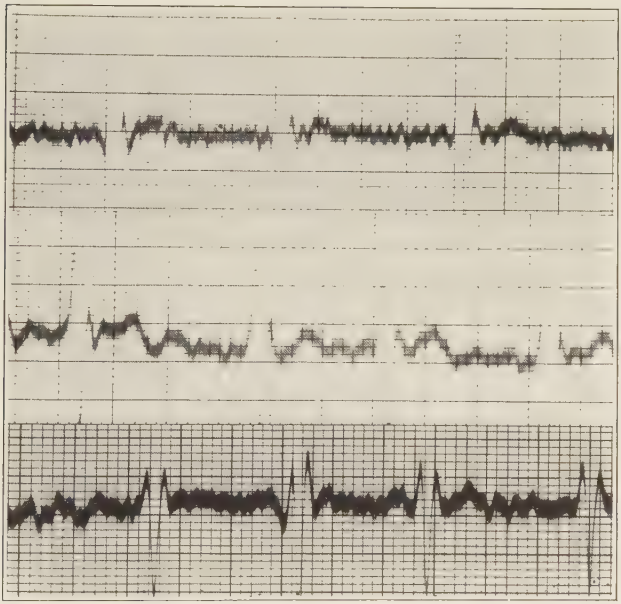

FIG. 32.—Case report No. 5. Nov. 11, 1923. Cardiogram showing left ventricular preponderance and auricular fibrillation.

CASE REPORT NO. 5.

Male, aged twenty-six years. Ex-soldier. Admitted to medical ward April 25, 1923.

Present Illness: In 1917, while overseas, had several "attacks" of nervousness with loss of weight, diagnosed as

"motor and psychic hyperexcitability with hyperthyroidism." Present symptoms dated from February, 1923.

Condition on Admission: Patient presented all of the symptoms of Graves' disease in an exaggerated form. He was extremely restless, talked volubly, and was unable to fix his attention. Tremor was marked; eye signs very evident, with a pronounced stare; expression wild. Pulse, 144, regular. Blood pressure, 170/70. T.C.D., 9.5 cm. No murmurs. Attempt to take basal metabolic rate failed because of lack of coöperation.

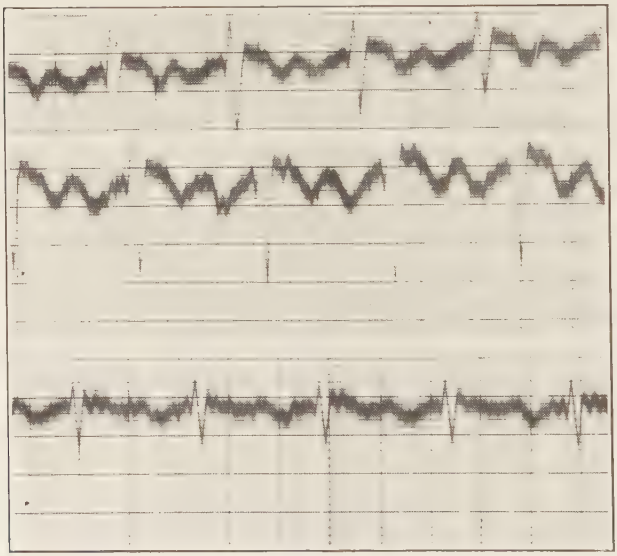

FIG. 33.—Case report No 5. June 4, 1926. Cardiogram from same case as Fig. 32, showing normal tracing.

Transfer to surgical service recommended, but delayed until June 9, owing to interference by patient's family. June 14, basal metabolic rate, +92.

Operation: On June 18 right upper polar ligation. On June 25, left upper polar ligation. On July 19 basal meta-

bolic rate, +65. On July 23 discharged, with instructions to return in six weeks.

Owing to further interference by his family the patient was not readmitted until October 30. In the interval there had been a gain of 30 pounds. Pulse, 110, irregular. T.C.D., 12 cm. Cardiogram (Fig. 32) showed left preponderance and auricular fibrillation. Basal metabolic rate, +63; weight, 145. Digitalis and Lugol's solution administered. November 6, basal metabolic rate, +52; weight, 145. November 14, basal metabolic rate, +17; weight, 154. November 22, basal metabolic rate, +1; weight, 157.

Operation: November 26, under local anesthesia, subtotal thyroidectomy. Uneventful recovery. December 7, basal metabolic rate −10.

June 4, 1926: Cardiogram (Fig. 33) showed normal tracing. Note the remarkable difference between this tracing and that taken November 11, 1923 (Fig. 32), when the auricles were fibrillating and the Q.R.S. groups were fairly characteristic of left ventricular preponderance.

February 4, 1928: Basal metabolic rate, −6; weight, 160; pulse, 72, regular. No tremor of hand or ocular signs. Has been working steadily since autumn of 1926.

TREATMENT OF GRAVES' DISEASE.

In the treatment of Graves' disease the medical profession are not of one mind. There are those who think that operation should never be resorted to; those who think that it should be resorted to only when rest in bed, iodine medication, and radiation have proved ineffective; and those who think that, in fully-established cases, operation should be performed without delay. While incipient cases may be cured by rest in bed and iodine, it has been our experience that patients with a well-established syndrome are rarely restored to normal health by these measures, and, upon resumption of active life or in the event of subsequent infection, are likely to develop a return of symptoms in an aggravated form. Cases of this type are especially susceptible to a sudden

relapse or to a crisis which may prove fatal, as is illustrated by the following report:

Case Report No. 6.

Female, aged forty years. Married. Admitted by ambulance to service of Dr. H. A. Lafleur, December 27, 1921.

Present Illness: In August, 1920, consulted family physician, who advised extraction of several infected teeth. Patient had not been feeling well and had lost weight. Extractions followed by improvement in health and gain in weight. In spring of 1921 had influenza. On October 10, 1921, again consulted physician, complaining of palpitation, nervousness, irritability, fatigue, and loss of weight. Thyroid enlarged; exophthalmos; pulse range, 120 to 136. An iodine preparation prescribed, which patient took until November 2, with improvement; there was a gain in weight, the pulse was slower, the exophthalmos less, and the gland smaller. Patient continued to go about and attend to her household duties. As she began to lose ground again, the iodine was renewed on November 16, but this time without evident benefit. It was later discontinued. From December 1, the patient was confined to the house, and for the greater part of the time to bed. On December 23, basal metabolic rate, +44. Patient became very excitable at Christmas.

Condition on Admission: Temperature, normal; pulse, 132. Very nervous and restless. During the night irrational and noisy; tried to get out of bed. Morphine, $\frac{1}{6}$ grain at midnight; repeated at 4 A.M.; only temporary relief.

Seen in consultation at noon, December 28. Extremely restless. Excoriation of skin over elbows and knees. Delirious. Temperature, 99.4° F.; pulse, 140. Face flushed. Marked exophthalmos and stare. Well-marked generalized enlargement of thyroid; consistence firm; pulsation and loud bruit.

Chloral hydrate given at 3 P.M. and 7 P.M., with good effect. Ice-pack at 2 P.M. temporarily arrested upward trend of temperature. Repeated at 9 P.M. At 10 P.M.

temperature and pulse began to rise rapidly; temperature, 106° F.; pulse, 180. Patient became comatose and died at 4.45 A.M., December 29.

Comment: The dysthyroidism in this case probably dated from August, 1920. The exophthalmos and firmness of the gland suggested chronicity.

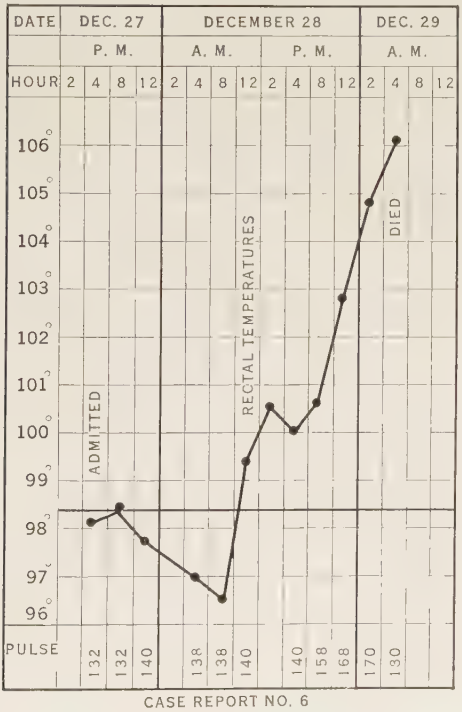

FIG. 34.—Chart of case report No. 6.

The following chart (Fig. 35) represents diagrammatically the metabolic curve in a chronic case treated by rest alone and the curve in a similar case treated with iodine and rest. It is to be noted that neither curve touches normal, and that

the rise in both curves, due to the increasing severity of recurring exacerbations, shows a definite parallelism.

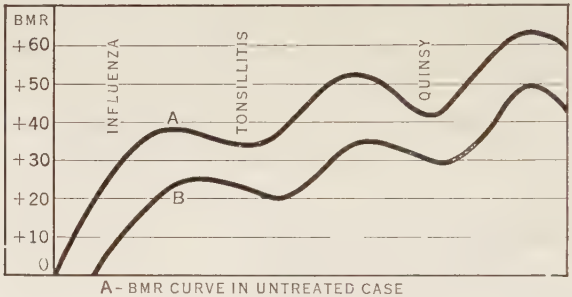

Fig. 35.

Although at the time that the Goiter Clinic at the Montreal General Hospital was established the risks of operation were very much greater than they are now, it was decided, after a careful analysis of the results of various clinics, not to allow patients an option between roentgen-ray treatment and operation. As far as one could determine from statistics, the ratio of cures from the two methods was about 3 to 2 in favor of surgery. The attitude taken at that time has been justified. Many patients have come to the clinic who have undergone roentgen-ray and radium treatment elsewhere, without improvement, and who in the meantime have sustained serious damage to the heart. Others, though distinctly benefited by roentgen-ray treatment, remain toxic. These patients are usually loath to undergo operative treatment, and often refuse to do so until an exacerbation of their symptoms convinces them of the futility of further delay.

End-results have proved that operation offers the surest hope of permanent recovery. As Kocher has pointed out, however, the earlier the intervention the more complete the cure; in other words, the success of the operation depends upon the absence of permanent cardiovascular changes. Early cases, those in which there has been but little nutri-

tional failure, respond promptly to thyroidectomy and recover without residual cardiovascular symptoms. There has been, too, in recent years a gradually diminishing mortality and a marked curtailment of the period of postoperative toxicity, due less to improved technique than to the administration of iodine before and after operation.

As a preliminary to treatment an exhaustive physical examination is essential. Each case must be analyzed individually, because only by clinical familiarity with the patient can one assess the operative risks. In order that examination may be as complete as possible, the following record form has been adopted in the Montreal General Hospital Clinic:

GOITER FORM NO. 1.

Date Outdoor No. Indoor No.
Name Address Goiter Clinic No.
Age S. M. W. Occupation
Referred by History taken by
Complaints
Family History
Personal History: Birthplace
Subsequent places of residence with dates
Menstrual History
Previous illnesses and operations
Habits: work rest exercise diet
Present Illness: Antecedent shock Infection Physical strain
Was there any thyroid enlargement in adolescence?
When was goiter first noticed?
Has it grown gradually, intermittently or abruptly?
Does it enlarge with menstruation, pregnancy or fatigue?
When were symptoms first noticed?
Chief Symptoms in Order of Onset, and general course of the disease:
Previous Treatment: Ointment Medicine Thyroid extract
X-rays Radium Operation
Result

PRESENT CONDITION.

Nutrition: Development: Facial expression
Color Mental state
Temperature Weight
Teeth
Tonsils: Hypertrophy of lingual tonsil
Subject to sore throat?
Hearing: Ringing in ears Dysphagia
Voice: Normal Husky Aphonia
Appetite: Normal Diminished Increased Variable
Bowels Diarrhea Vomiting
Dyspnea Cyanosis
Cough Fever

SYMPTOMS OF HYPERTHYROIDISM.

Skin: Moist or dry? Sweats Flushings Erythema
Tremor: hands lips tongue Palpitation Precordial thumping
Nervous Restless Irritable Insomnia Headache
Heat intolerance: Edema of ankles Falling of hair
Loss of weight: lb. since
Loss of strength Quadriceps weakness
Ocular signs: Exophthalmos Widening of palpebral fissure
Lagging of upper lid Lack of convergence
Infrequent winking Wrinkling of forehead
Pigmentation of lids Irregularity of pupils
Epiphora Glistening cornea

GOITER.

General appearance, contour
Position
Mobility
Unilateral (right left) Bilateral Isthmus Consistence
Homogeneous or nodular Tenderness Palpable lymph glands:
Pulsation Thrill Bruit
Circumference base of neck
Compression of trachea Displacement of trachea

Pulse: Rate Regular? Volume
Heart: Transverse cardiac dulness Retrosternal dulness
Sounds
Blood pressure

Clinical Diagnosis:

Adolescent	Adenoma non-toxic
Late colloid	Adenoma toxic
Graves' disease	Thyroiditis
Combined Graves' and adenoma	Strumitis
Iodine thyrotoxicosis	Malignant

Treatment recommended

Since the practice of administering iodine as a preoperative measure has been introduced, it has been possible to give preparatory treatment in their homes to many patients who, owing to the paucity of beds, cannot be taken into hospital immediately. This home treatment has effected a marked curtailment in the period of preoperative residence in hospital.

Supervision of home conditions is undertaken by the Social Service Department, when necessary. It is futile to give the working mother of a large family a prescription for

Lugol's solution and instruct her to go home and rest until a bed is vacant. If such a patient is to rest, in the medical sense of the word, she must be relieved of household work and the constant small irritations and anxieties which attend the care of children.

Under satisfactory home conditions improvement may be looked for. The promptness with which the nervous phenomena are relieved is most striking. There occurs also a fall in the pulse rate, an increase in weight, and a return of strength. Other factors being favorable, one may expect that within from ten days to three weeks the basal metabolism will drop to a safe level for operation. This rapid restoration to a feeling of well-being may lead patients to believe that a cure has been effected and that operation is unnecessary. It must be impressed upon them that iodine is rarely curative, that the condition is likely to recur in a more exaggerated form, and that operation in the early stage of the disease gives the best prospect of cure.

The removal of the patient from home to hospital, for metabolic tests or operation, should not be undertaken lightly. Cases of the fulminating type or chronic cases going through a crisis call for the exercise of good judgment on the part of the family physician or consultant. There is always an exacerbation of symptoms for a few days after admission, and undoubtedly a fair prospect of surviving a crisis has in many cases been extinguished by the strain of a journey to hospital.

The preoperative administration of iodine has proved a boon also in hospital. The tranquillity which it has brought to the atmosphere of the thyroid ward is comparable to that effected by the cold bath in the typhoid ward.

Although introduced by Plummer as early as March, 1922, we are still speculating as to how the preoperative administration of iodine abolishes so promptly the serious nervous phenomena and prevents the postoperative crises which were so familiar to the surgeon who had the courage to operate prior to its introduction. We may, however, with some

justification construct a theory upon metabolic and clinical observations.

As already stated, the thyrotoxicosis in Graves' disease is thought to be due in part to excess production of physiological secretion and in part to the elaboration of an abnormal hormone. With the administration of iodine, it is thought, the percentage of normal product in relation to the percentage of toxic or qualitatively abnormal product gradually increases, and in time the thyrotoxicosis comes to be for the greater part a true hyperthyroidism. From experience we know that

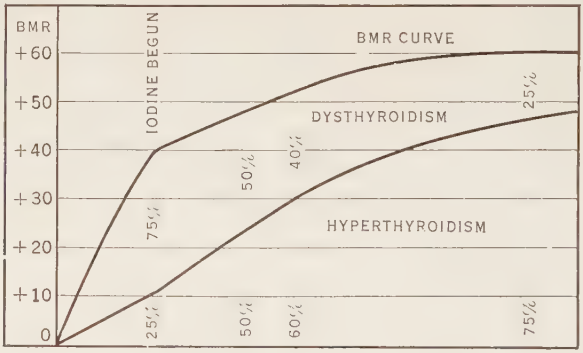

FIG. 36.—The upper line represents the total hypersecretion as measured by the basal metabolic rate. Note the deflection toward the horizontal after iodine therapy begun. The lower line represents the rise in normal physiological secretion after the commencement of iodine therapy.

patients who in the early acute stages have a metabolic rate of say +50, and who, if immediately operated upon, would probably die, may later, after a course of iodine, present none of these severe nervous symptoms, though the rate may be the same or even higher, say +60, and may undergo operation without danger of a postoperative reaction. The theoretical explanation of this change in symptomatology and general aspect is that the iodine has largely corrected the dysthyroidism and that the persistence of a high basal metabolism is due chiefly to a pure hyperthyroidism.

The chart, Fig. 36, may convey the argument more clearly.

Until the basal metabolic rate has been estimated accurately, it is our routine practice, in both indoor and outdoor cases, to prescribe five minims of Lugol's solution, well diluted, three times a day with or after meals. A clinical estimate of the rate of metabolism can be made with a fair degree of accuracy upon the general condition and the pulse rate. If the basal metabolism proves to be between + 60 and +80, the dosage is increased to 10 minims three times a day; if above +80, to 20 minims three times a day. To hospital patients who are unable to coöperate in the taking of a basal metabolic rate because of delirium or poor cerebral control, the maximum dosage is given. This is reduced if necessary when the rate is taken.

The parallel rise and fall of the metabolic and pulse rates in some cases is exemplified by the following chart (Fig. 37), taken from one of our case histories. This close parallelism, however, is met with only in patients with good cerebral control. While the pulse rate is affected by the emotions and by various afferent impulses, including ocular and aural, the basal metabolism is not so affected. The chart shows (1) the fall in basal metabolism and pulse rate as a result of rest in bed; (2) the fall in both metabolism and pulse rate following bilateral ligation; (3) the coincident rise in the metabolism and the pulse rate with the onset of menstruation, which was accompanied by a very pronounced increase in the size of the gland; (4) the close parallelism in the decline to normal of the basal metabolism and the pulse rate following thyroidectomy. It is, of course, fallacious to assume that the basal metabolic rate is the only accurate measure of toxicity, but it is undoubtedly the most accurate single index of the degree of toxicity, as well as of the trend of the attack and the effect of therapeutic measures, medicinal or surgical.

In crises attended with vomiting and diarrhea, excessive nervousness, and delirium or delusions, one must act promptly

and vigorously. Frequently iodine cannot be administered by mouth. If there is no diarrhea, the rectal route may be tried. If this method is not feasible, iodine in the form of Lugol's solution should be given intravenously in 20-minim doses every six hours with 5 per cent glucose saline.

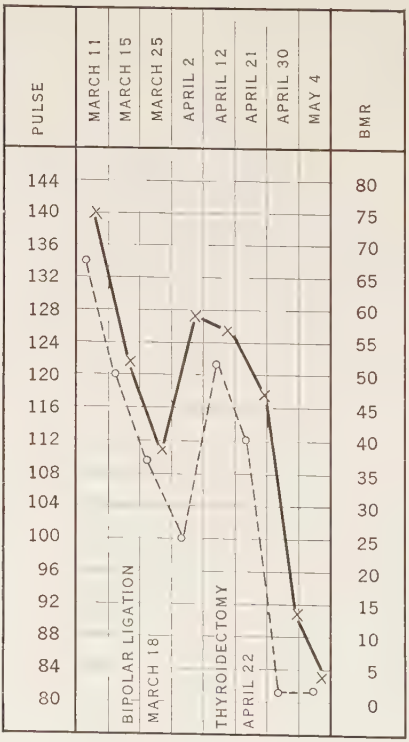

Fig. 37.

Caffeine is effective in sustaining circulation in critical cases, though it is apt to induce sleeplessness. Camphor oil is also of value. In the absence of arrhythmia digitalis or digitaline is of little benefit. The most valuable cardiac

stimulant is a 10 per cent glucose saline, given intravenously. Small amounts, 300 to 350 cc., given every six hours, are to be preferred to a full saline of 600 cc. given at longer intervals; the frequent administration sustains the heart muscle and the smaller amount may be given without fear of producing cardiac dilatation. Other drugs which are of value in crises and in the early stages of severe cases are morphine hypodermically, bromides per rectum, luminal in $1\frac{1}{2}$ grain doses, and chloretone in 10-grain doses.

Unfortunately there are still crises in which no known therapeutic measure is effectual.

In severe toxicity the ice-pack is a most valuable adjuvant. It relieves restlessness, lowers the pulse and metabolic rates, and induces sleep. It should be given twice daily, for ten minutes at a time. Patients at first dread these treatments, but later ask that they be continued because of the feeling of well-being which they induce. There follows a list of the requisites for such treatments, with a description of the method of administration.

Ice–pack.

Articles Required:

4 Flannelette blankets.
1 Rubber sheet.
Crushed ice.
Pail of water 80° to 85° F.
Ice-cap.
Hot-water bag.

Method:

Place ice-cap on head.
Remove upper bedclothes and replace by (1) flannelette blanket. Place under patient rubber sheet covered with (2) flannelette blanket. Wring out (3) flannelette blanket in cold water, fold once and place under patient.

Wring out (4) flannelette blanket in cold water and wrap well around patient, so that no two surfaces of the body are in contact with each other.

Sprinkle ice over and around patient. Use only crushed ice and watch the patient carefully. Use a certain amount of friction throughout the duration of the pack—ten minutes. Hot-water bag to feet.

It is a moot point whether a focus of infection, such as diseased tonsils or infected teeth, should be dealt with before or after thyroidectomy. The wide divergence of views on this point may be due to the fact that the severity of Graves' disease varies greatly in different countries. In mild types where there is a possibility of cure without thyroidectomy, we agree with Eason that the elimination of such foci should be the first consideration; but in a severe form of Graves' disease it is our opinion that the major condition should always be dealt with first, not only because tonsillectomy may be followed by a severe reaction or crisis, but also because, if thyroidectomy is postponed, myocardial changes may develop. If a serious surgical risk is to be assumed, it should carry with it the promise of cure and not simply of palliation. Furthermore, if after the basal metabolism has been brought to a safe level for operation thyroidectomy is postponed in favor of tonsillectomy, the opportunity for saving the patient may be permanently lost. The fall in the metabolism under iodine treatment is too often but temporary, and at any time operation may be barred by a crisis, or may have to be undertaken at a later date under less favorable conditions. (See Case Report No. 18, page 157.)

As soon as thyroidectomy has been performed and the basal metabolism restored to normal, tonsillectomy or dental extractions, if indicated, may be performed without hazard, and should certainly be carried out.

The two most vital points in the surgical treatment of Graves' disease are: (1) the time at which the operation is

performed in relation to the general status of the case, and (2) the extent of surgical interference.

In the average case a week's course of Lugol's solution suffices to bring the basal rate down below +50, to effect a corresponding improvement in the pulse rate, to lessen the restlessness, and to abolish the stare. This is ordinarily a safe time to operate, but in cases in which there has been marked failure of nutrition operation should be postponed until there has been a definite gain in weight. Only clinical familiarity with these patients enables one to determine with unerring judgment their fitness or unfitness for operation.

One cannot overemphasize the importance of accurately assessing the condition of each individual patient before operation, and at the same time determining in one's mind how much should be done at one time. While the preoperative administration of iodine has rendered the one-stage operation feasible in most instances, there are still cases in which one can avoid operative fatalities only by doing a preliminary ligation or unilateral lobectomy. Once the extent of interference warranted by the patient's general condition has been decided upon, it is a great error to extend the prearranged plan of operation, no matter how favorable the patient's condition may appear to be while on the table.

On the whole it has been found a disadvantage not to advise patients of the time of operation. With the disappearance of severe nervous symptoms patients are, in our experience, always ready and waiting for operation. The best plan is to inform them three or four days ahead of time. In the interval the more apprehensive adjust themselves to the impending event. Only rarely now is it necessary to operate upon patients in their beds.

On the day preceding operation the hair is washed or, if this has been done within a few days, it is thoroughly brushed with a damp brush to get rid of the dust. This procedure is a definite safeguard against infection at operation.

The iodine dosage should be doubled on the day before, the day of, and the day after operation.

On the evening before operation the patient is given 5 grains of veronal. The neck is washed with petrolic ether and alcohol and painted with a 2.5 per cent alcoholic solution of iodine. A sterile towel is bandaged about it. The patient is encouraged to take fluids freely until two hours before operation. One hour before operation 10 grains of chloretone is administered, and this dose is repeated half an hour later. Vomiting after the administration of chloretone is rare, while after morphine it is common. On the table the neck and shoulders are again prepared and the patient draped.

As a routine procedure we employ local anesthesia only. For thyroid work general anesthesia presents many disadvantages: the presence of an anesthetist adds to the risk of wound infection; engorgement of the cervical vessels occurring at intervals increases the oozing and obscures the field; the surgeon is deprived of the coöperation of the patient in testing from time to time the conductivity of the recurrent laryngeal nerves; and the handling of the tissues is inevitably accompanied by more traumatism than when local anesthesia is used.

In the case of a few patients, who either had poor cerebral control or refused to undergo operation without a general anesthetic, open ether or nitrous oxide, combined with local infiltration, was employed. Ether is preferable to nitrous oxide, because it does not cause cyanosis. Prolonged cyanosis, implying as it does defective oxygenation of the cardiac muscle, is a serious matter. While nitrous oxide and oxygen is theoretically an ideal anesthetic, it is seldom administered in an ideal way.

In some clinics ethylene is considered to be a distinct advance upon both ether and nitrous oxide. It too, however, has the disadvantage of rendering the patient unconscious and incapable of vocalization at the request of the surgeon. It has not been used in the Montreal General Hospital Clinic.

For the skin incision we use 1 per cent novocain, and for the deeper injections 0.5 per cent novocain. Adrenalin should not be used in toxic cases. In the early days of the clinic it was added to the novocain solution for the skin incision. During this period there were 3 sudden deaths on the table, all occurring shortly after injection and before operation had proceeded beyond the stage of exposure. These experiences led Dr. Rabinowitch to make observations upon the effect of adrenalin upon the basal metabolic rate of normal subjects, and he was able to show that an average rise of 22 per cent occurred within fifteen minutes of injection. It is probable that in toxic subjects the rise in metabolism would be much more pronounced. Since discontinuing the use of adrenalin we have had no deaths on the table.

The performance of thyroidectomy is now so thoroughly standardized and has been so fully described in numerous text-books that it is unnecessary here to do more than add a few comments to the illustrations.

One and the same operative procedure should not be slavishly followed in all cases. The safety of the patient should be the first consideration.

In placing the skin incision one should aim at an adequate exposure of the upper poles. Otherwise it is difficult, and in some cases (where a lobe—usually the right—extends high into the neck) impossible, to ligate the superior vascular pedicle and remove the apex of the lobe. The incision should be carried through the skin and subcutaneous tissue and flaps reflected. The platysma should not be divided. If, however, it is for any reason divided, it must be sutured separately, if a narrow scar is to be secured. Failure to suture the divided platysma is the commonest cause of a wide scar. The upper segment should always be threaded upon the needle first. If this order is reversed, the upper skin flap will override the lower, with the production of an unsightly line of union.

While the split fascia operation, with retraction of the

prethyroid muscles, is the one which is generally employed in the Montreal General Hospital, especially when the lobes are small and freely movable, transverse division of the prethyroid muscles, the sternohyoid and the sternothyroid, is always practised if there is any difficulty in securing adequate

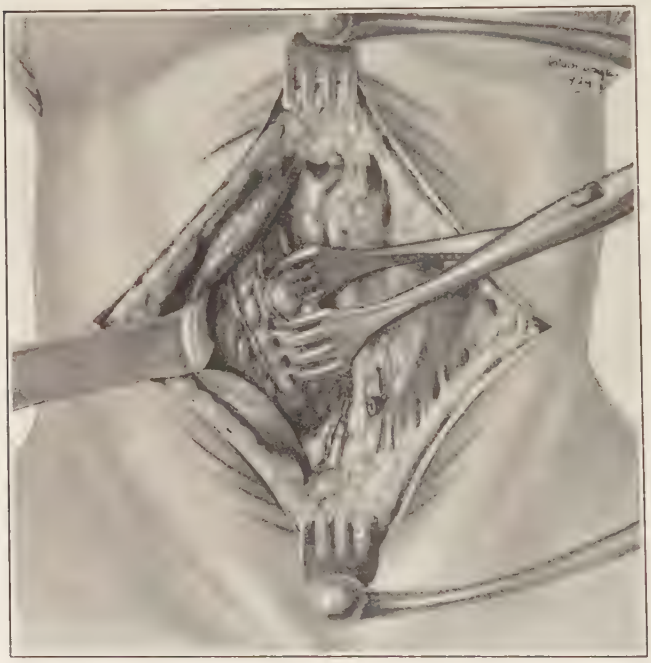

FIG. 38.—Showing retraction of the platysma and prethyroid muscles on the right side after division of the median aponeurosis, with exposure of the right lobe.

exposure. If one employs muscle retraction as a routine procedure, one is certain in time to encounter troublesome hemorrhage or embarrassment of respiration from lateral pressure upon the trachea. For the less experienced operator, too, muscle division is the method of choice, although undoubtedly the division of these muscles and the large

venous trunks which lie upon them increases the subsequent serous exudation (Figs. 38 and 39).

In order to expose the vessels it is necessary to strip off the capsular attachment of the sternothyroid muscle at the

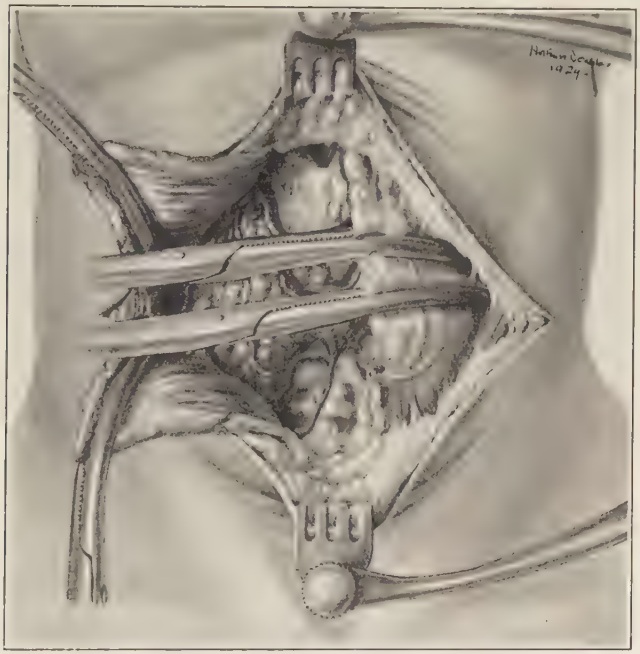

Fig. 39.—Showing (*a*) transverse division of the prethyroid muscles on the right side, with exposure of the right lobe, and (*b*) the position of clamps prior to division of these muscles on the left side. Free mobility in the muscle flaps is secured by a high division and by excluding from the tips of the forceps the anterior margins of the sternomastoids. In practice the clamps are placed as close together as possible.

upper pole, and in order to prevent secondary hemorrhage or hemorrhage during operation the vascular pedicle of the upper pole must be securely ligated. Furthermore, the apex of a lobe must not be left behind. As has been mentioned in the chapter on Anatomy, the upper pole is the most fixed point,

and its delivery is therefore difficult. Failure to deliver the upper pole, however, especially in cases where it overlies the vascular stem, frequently prevents the removal of sufficient tissue and the ligation of all branches of the artery. In consequence the ultimate result of operation may be unsatisfactory, either because too much tissue is left behind or because, owing to the excessive blood supply, the stump hypertrophies. In freeing the upper pole one should not forget its close relation to the internal jugular vein.

The lower poles must also be exposed. Downward extension of a lower lobe behind the sternoclavicular joint is extremely common and a large residue in this location is sufficient to maintain toxicity. Furthermore the amount of gland tissue to be left behind cannot be estimated unless exposure is complete. This can be effected without traumatism to the recurrent laryngeal nerve.

While speed in thyroid operations is desirable, time spent in securing complete hemostasis is generally justified. The superior thyroid arteries should be ligated and ligatures placed upon the lateral capsular branches of the inferior thyroid arteries.

If one is to secure uniformly good results and restore the patient to a normal physiological status, it is essential that, with few exceptions, operation should be radical. A great deal has been recorded about the amount of gland tissue removed, but very little about the amount left behind. The term "subtotal thyroidectomy" should imply the removal of the whole of the thyroid gland with the exception of a mass of tissue on each side equivalent in volume to one-third of a normal lobe, which is estimated roughly to be equivalent in volume to the terminal phalanx of the little finger, or by measurement 3 cm. long and 1½ cm. thick. While this is the routine procedure, removal should be less radical where the gland tissue on incision suggests advanced involution as the result of prolonged iodine treatment. On the other hand, in long-standing cases with advanced myocardial changes

(auricular fibrillation) it is our practice to leave behind less than the usual amount of gland tissue, in order to maintain the metabolism constantly below normal, with the object of husbanding the cardiac reserve.

The finding of acidophilic cells in the tissue from cases in which a single preliminary lobectomy has been performed may be a guide in determining whether further tissue removal is warranted (Smith).

Removal by sharp dissection is the method of choice. It leaves a clean-cut untraumatized surface and one can estimate more accurately the amount of tissue left behind.

The view that complete thyroidectomy should be performed and subsequently thyroid gland preparations administered to prevent myxedema is, we think, to be rejected. Not only is there greater risk of injuring the recurrent laryngeal nerves and parathyroids, but thyroid preparations are not an adequate substitute for active glandular secretion, especially during the first year and a half or two years. During this period, although the basal rate may be normal, it is difficult to maintain body weight and nutrition. Gland preparations cannot provide that elasticity of function which is possessed by the gland itself.

Hemorrhage at operation is now rare. It is usually the outcome of an inadequate exposure, which necessitates the ligation of the superior thyroid vessel under tension. The stretched vessel occasionally retracts when the clamp is released. Another cause of hemorrhage is injury to the internal jugular vein, a point which has already been dealt with. Ligature of the lateral capsular branch of the inferior thyroid artery is an added protection. It is inadvisable to ligate the main trunks of the inferior thyroid arteries, because these vessels supply the parathyroid nodules directly and their ligation may cause tetany. Oozing is usually controlled by the approximation of the inner and outer margins of each remaining plaque of thyroid tissue with interrupted stitches of catgut, a face-to-face suture. In some cases suture of the

outer margin of the plaque to the exposed lateral wall of the trachea is effective. Even if there is no oozing, it is always desirable, if possible, to cover the incised surface of the lobe. In no case have we found it necessary to pack the wound and do a secondary closure.

Adhesions resulting from roentgen-ray or radium treatment do not seriously prolong operation, though they increase the danger of injury to the jugular vein during exposure. One's anxiety in these cases is with regard to the healing process rather than the operative procedure. After prolonged roentgen-ray or radium treatment the nutrition of the tissues of the neck may be so impaired by fibrosis that healing may be delayed for weeks. Sloughing is frequent and infection the rule.

If the prethyroid muscles have been divided, they should be sutured with a lock-stitch of plain catgut. If the aponeurosis has been split, it should be brought together in the median line with three or more interrupted stitches of fine catgut. In closing the skin wound we have found it an advantage to employ three interrupted subcutaneous catgut stitches to approximate the margins of the wound and Michel clamps to bring the skin edges accurately together. The clamps are removed at the end of forty-eight hours.

In secondary operations the exposure of the gland may be difficult, owing to excessive scar tissue. In such cases one should always divide the prethyroid muscles and in the dissection take care to keep constantly upon or just within the thickened capsule. The chief menace in these operations is hemorrhage from the internal jugular vein. As the remnant of the lobe is withdrawn, the collapsed vein adherent to the capsule is liable to be exposed and incised longitudinally. In such an event the vein should be isolated and ligated both above and below the point at which it has been injured.

It is now our practice to close the wound without drainage, a practice which has greatly reduced the frequency and duration of postoperative serous discharge. In cases of

persistent oozing, however, a cigarette drain, with wick soaked in adrenalin, should be inserted. The adrenalin is not absorbed. The oozing gradually lessens and the wick can usually be removed at the end of twenty-four hours, but in cases of high blood pressure, or following secondary operations where scar tissue is excessive, it may be necessary to leave the drain in for several days.

POSTOPERATIVE TREATMENT.

Pain is controlled by hypodermic injections of morphine $\frac{1}{6}$ grain, or heroin $\frac{1}{12}$ grain, every six hours. To prevent dehydration and promote renal action, 6 ounces of 5 per cent glucose saline is given per rectum every four hours until the patient can swallow without discomfort. Iodine is included in the salines as a routine, digitalis when indicated, and bromides when necessary to control restlessness. In myocardial cases (auricular fibrillation) 1 dram of digitalis in the form of the tincture is given in the first saline, repeated in twelve hours, and thereafter continued by mouth (10 to 20 minims every six hours), providing the stomach is tolerant. From 4 to 8 ice-bags are placed about the patient and these are a great comfort. Cough is controlled by the administration of codein as occasion requires. Liquor ammoniæ acetatis, in dram doses given every three hours, loosens tenacious mucus and lessens the effort of expulsion. Patients find it very restful to be turned over on the right side from time to time. Visitors should be excluded during the first forty-eight hours.

Secondary hemorrhage should be a rare postoperative complication, but, if it does occur, one should never temporize. The patient should at once be taken to the operating room, the wound opened, and the bleeding point found and ligated. In severe cases transfusion is indicated after the hemorrhage has been arrested. Restoration of the blood volume hastens convalescence and promotes healing. In

our series of 689 operations (for adenomatous as well as Graves' disease) postoperative hemorrhage, with infiltration of the neck and acceleration of the pulse, occurred in only 2 cases. These patients subsequently made uninterrupted recoveries.

As a rule the peak of the postoperative febrile reaction occurs from twelve to thirty-six hours after operation. In a recent case the reaction was delayed until the third day after bipolar ligation—the latest postoperative crisis which we have seen. (See Case Report No. 7, page 135.) Although the preoperative use of iodine has largely abolished these reactions, they occasionally occur, usually unexpectedly, and must be combated by every means at one's disposal.

If in spite of the postoperative administration of iodine, morphine and bromides, and the application of ice-bags to the trunks and extremities, extreme restlessness and a rapidly rising temperature (above 103° F.) should supervene, one should not hesitate to employ the ice-pack. Renal excretion may be stimulated by intravenous salines given every four or six hours.

A sharp falling-off in the volume of the pulse is best met by the intravenous administration of 10 per cent glucose saline. As already stated, large intravenous salines, because of the strain they put upon the heart, are to be deprecated. All saline solution for intravenous use should have been prepared within forty-eight hours. A rapid pulse after operation, that is a pulse between 140 and 180, is not necessarily a serious omen. If there is no air hunger and no cardiac dilatation, if the heart sounds are good and the patient's color and expression normal, a pulse rate of even 200 may be sustained for twenty-four or forty-eight hours without ill effects. If the pulse becomes irregular, digitalin $\frac{1}{50}$ grain every six hours should be administered hypodermically.

Postoperative infections are uncommon. With one exception, those in our series were of a mild type and developed

either after prolonged serous discharge or after delayed healing due to preoperative damage to the tissues by roentgen-rays or radium. The exception was an acute streptococcus infection which followed immediately upon operation and ended fatally. (See Case Report No. 15, page 155.)

One should be constantly on the look-out for retained serum. This should be evacuated once or twice daily with a director, care being taken to maintain a strictly aseptic technique.

Case Report No. 7.

Female, aged twelve years. Admitted December 28, 1927, with diagnosis of Graves' disease.

Present Illness: Goiter present for three months. Symptoms for four months.

Condition on Admission: Marked generalized enlargement of thyroid. Pronounced tremor of hands, lips and tongue. Definite stare. Slight exophthalmos. Edema of upper lids. Pulse, 152. Transverse cardiac dulness, 14 cm. Basal systolic murmur. Basal metabolic rate, +74. Cardiogram showed tachycardia, rate 225 to 240 per minute; P and T waves superimposed; that is, complete absence of diastole.

Preoperative Treatment: Lugol's solution, 5 ♏ t.i.d., gradually increasing to 10 ♏ t.i.d. January 4, 1928, basal metabolic rate, +48; pulse, 116. Marked general improvement. January 7, basal metabolic rate, +48; pulse, 128. January 10, basal metabolic rate, +49; pulse, 126.

Operation: January 11, under gas-oxygen anesthesia, bilateral polar ligation. Pulse before, 136; after, 148.

Postoperative Course: Temperature rose from normal on second day postoperative to 103.6° F. on third day postoperative; the pulse from 146 to 196. Until death at 3 P.M. on sixth day postoperative, temperature range 101° to 104° F., and pulse range 184 to 210. The postoperative treatment consisted of intravenous glucose salines, morphine, bromides, iodine, ice-bags and cold spongings.

Autopsy Findings: Hyperplastic thymus. Fatty infiltration and degeneration of the liver. Adenoid goiter (the tissue of Graves' disease).

Goiter Form No. 2 is here shown. This form includes a note on the preoperative condition, operative and postoperative details, and a synopsis of the written instructions given to the patient on discharge.

Goiter Form No. 2.

Name Indoor No.
Date of admission
Condition on admission
Number of days preoperative rest
Preoperative treatment and medication
Electro-cardiogram
Roentgen-ray of upper thorax
Urinalysis
Basal metabolic rates (before operation)
Blood: R.B.C. Hemoglobin %
Differential, P.M.N. % Small Lym. % Large Lym. %
Trans. % Eosin. % Mast. %
Biochemical, Sugar % Urea N. mg. per 100 cc.

Weight in
Operation: Date
Ligation single, right left Ligation double
Lobectomy: Right Left
Subtotal excision
Anesthesia: Local
General { gas-oxygen / ether
Combined local and general

Drainage days.
Reaction: Slight Moderate Severe Vomiting
Wound Healing: Primary
Infected
Hemorrhage
Serum Days
Clips removed

Postoperative Treatment and Medication
Complications
Pathological report
Basal rate (postoperative)
Weight out
Date of discharge
Condition on discharge
Instructions given to patient on discharge
Rest
Diet
Medication

Iodine medication, averaging 5 ♏ morning and evening, is continued for ten weeks after operation, except in those cases with a normal postoperative metabolism in which the microscopic examination has shown advanced iodine involution or the presence of large numbers of acidophilic cells. All patients are given a bitter tonic containing nux vomica and gentian, to be taken before meals for one month, and an iron tonic, usually in the form of Parrish's Chemical Food, to be taken after meals for a period of two weeks. The prolonged use of iron is apt to cause indigestion.

Care of the feet after the period of bed-rest is of great importance. The gain in weight and the edema of the lower leg which often develops when the patient begins to walk about reduce the strength of the plantar arch. The patient is instructed to wear a substantial shoe with a reinforced arch or an adjustable plantar arch support (Scholl's) as soon as he begins to go about, and not bedroom slippers. Massage of the feet and legs, as well as exercises which strengthen the perineus longus and plantar flexors of the foot, are also of great benefit.

The appended instruction sheet covers the orders given to a postoperative case of Graves' disease of average severity.

INSTRUCTIONS FOR .....
(Name of patient)

Rest: Absolute rest in bed until (one month after discharge).
(Date)

Up and about gradually on one floor without any stair climbing until (two months after discharge).

Shoes: Bedroom slippers must not be used on getting up. Instead, wear a pair of substantial shoes with low heels—boys' brogues are best—and a pair of Scholl's foot-ease plates.

Pulse Keep a daily record of your morning and evening pulse and send it every four weeks to ———— Count the pulse as soon as you wake up in the morning and just before you go to sleep. (Never count it immediately after eating or after exertion.)

Diet: A liberal diet including whole wheat bread, whole milk, fresh fruit, cocoa, a fresh green vegetable daily (cabbage, spinach, lettuce, celery, cauliflower, peas, beans, etc.) and sea-food three times a week (halibut, haddock, salmon, mackerel, cod, etc.—fried or baked, but not boiled).

Medicine: As prescribed. Do not take more or have it renewed without instructions.

Follow-up Visits: At the end of your period of rest report personally or by letter to . . . . . .

Your case should be followed up for three years; you are therefore asked to report any change of address.

While one expects within two or three weeks of operation, that is at the time the patient leaves hospital, a recession of all symptoms of dysthyroidism, manifested by a normal basal rate, a steady hand, a normal pulse, and a marked improvement in the eye signs, a much longer postoperative rest period is necessary for the complete elimination of toxic products, the stabilization of thyroid function in the gland residue, and the restoration to normal of the heart muscle and general nutrition. To this end it is essential that the patient should be at complete rest—in bed, in a hammock, or on a sofa for four or six weeks after returning home, and at partial rest for a further period of one month. Rest even beyond the allotted period, followed by graduated walking exercise, is necessary in some cases for the complete recovery of the heart muscle, which, though clinically normal, may

prove upon exertion to have suffered an impairment of functional reserve. The resumption of office or household duties should be gradual and should not be permitted during warm

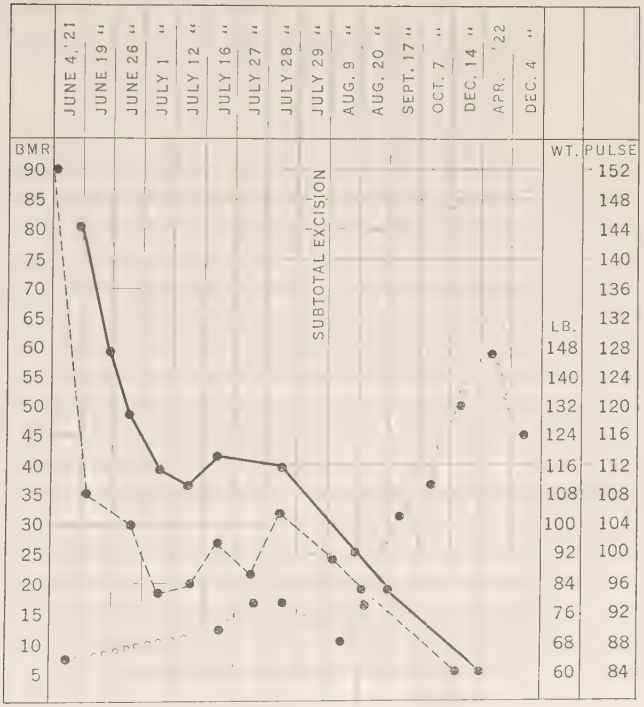

FIG. 40.—Chart showing rise in nutritional curve with fall in the basal metabolism. In this particular case (one of Graves' disease in an adult male of small stature) the emaciation at time of operation was extreme. Minimum weight, 64 pounds. Maximum postoperative weight, 146. Normal weight, 120.

Basal metabolic rate———— Pulse..... Weight ooooooo

weather, even at the end of the period of rest. If too great a demand is placed upon the thyroid remnants in the early postoperative months, compensatory hypertrophy is apt to ensue, with a recrudescence of symptoms.

Frequent follow-up examinations including basal tests have shown conclusively that the average case of Graves' disease does not, even under the most favorable conditions, achieve a normal physiological status in less than a year from the time of operation. Beyond question the year-end results are always much more satisfactory in those who have been able and willing to adhere strictly to the instructions given on discharge and at later follow-up examinations.

Subsequent to operation it is essential that these patients should be protected from the factors which were, presumably, responsible for the initiation of the dysfunction. Pregnancy should be avoided for two years. Infected teeth, diseased tonsils, or other foci of infection should be eliminated, physical strain avoided, and ample hours of rest and a suitable diet assured.

RECURRENCE.

If the basal metabolism does not fall to normal during convalescence or if after having been normal during the rest period it begins to rise as soon as the patient resumes his physical activities, it is evident that the operation has not been sufficiently radical. This should not be styled a "recurrence," but rather a "continuation" of the disease. Of the 334 patients in our series 13 had continued postoperative symptoms of thyrotoxicosis, and were ultimately cured by secondary operation.

The term "recurrence" should be restricted to those cases which have been radically treated, but in which, after a postoperative lapse of several months or even years without symptoms, there develops a gland hypertrophy which is uncontrolled and leads to the formation of a palpable tumor, with return of symptoms. This tumor is generally unilateral and at the upper pole, and may closely simulate adenoma.

In these cases it is seldom possible to restore the gland function to normal and stabilize the pulse and metabolism by further iodine-and-rest treatment. It is our practice to

advise the removal of further gland tissue, and the results obtained have fully justified this advice.

Eight of the 334 patients in our series underwent secondary operations for recurrence, and 2 of these had to submit to a third operation for recurrent hypertrophy for which no adequate cause could be determined. An analysis of these 8 cases follows:

1. Recurrence nine months postoperative. Attributed to premature resumption of housework.

2. Recurrence one year postoperative. Following attack of influenza.

3. Recurrence one year postoperative. Without determined cause.

4. Recurrence three years postoperative. Attributed to physical strain.

5. Recurrence four years postoperative. Attributed to physical strain.

6. Recurrence five years postoperative and again six years postoperative, without determined cause.

7. Recurrence two years postoperative and again seven years postoperative, without determined cause.

8. Recurrence seven years postoperative. Attributed to physical strain.

The following account of a recurrence of symptoms after a period of six years and three months, during which time the patient was in robust health, illustrates the importance of prolonged follow-up records in cases of Graves' disease. Statistics of cures based upon a twelve-months follow-up observation are not wholly reliable.

Case Report No. 8.

Female, aged twenty-eight years, married. Housewife. Admitted March 9, 1921.

Present Illness: Full Graves' syndrome. Goiter of large size. Present for two years. Symptoms for one year. Basal metabolic rate, +75.

Operation: March 18, bipolar ligation. April 22, subtotal thyroidectomy. Uneventful recovery.

May 4, 1921, basal metabolic rate, +4. Subsequently examined in clinic from time to time. Always free from symptoms. On March 7, 1927, weight, 225; neck perfect; no hypertrophy in stumps; no eye signs; no tremor; pulse, 78. Three pregnancies since operation. Youngest child aged three months; nursing. Patient doing all her own housework including washing. Advised removal of infected teeth.

In July, 1927, noticed enlargement of right side of neck. On September 28, basal metabolic rate, +39; weight, 222; pulse, 120. Fine tremor of hand. Palpable enlargement of upper pole of right lobe stump. Slight eye signs. Instructed to wean baby (now ten months old), to have two hours rest in afternoon, and to take Lugol's solution, 5 ♏ t.i.d. On October 26, this reduced to 2 ♏ t.i.d. On December 7, weight, 236; pulse, 100; basal metabolic rate, +6. February 8, 1928, weight, 240; pulse, 96; basal metabolic rate, +12. No complaints. No subjective symptoms. Enlargement of right lobe much less evident. Lugol's reduced to 2 ♏ once daily.

Seen on October 3. Had had dental extractions, as recommended. Feeling perfectly well. No tremor. Only slightly palpable enlargement of right lobe stump.

Comment: There are here four factors which may be held responsible for the gland hypertrophy and return of symptoms: frequently repeated child-bearing, prolonged periods of lactation, increasing household cares, and dental infections. It is probable that permanent stability will be secured only by further gland removal.

Residual symptoms other than hyperthyroidism are due to permanent cardiovascular changes or to ingrained autonomic instability. Although in some cases of Graves' disease the appearance of permanent myocardial changes is indefinitely postponed, such changes may be forestalled with certainty only by early operation. Attention has elsewhere been drawn to the fact that patients in whom an unstable autonomic

system was the predisposing factor in the development of the dysthyroidism are unrelieved of this instability by operation.

In chronic cases exophthalmos not infrequently remains as a permanent deformity. This is probably due to a deposit of fat in the orbit. In rare cases, in spite of the normal physiological status of the patient, the exophthalmos is progressive, owing to a further increase of fat within the orbit or to excessive sympathetic stimulation. Of interest, too, are

FIG. 41.—Eye signs developing first in right, later in left eye, (Graves' disease).

those cases in which exophthalmos develops first in one eye and later in the other, remaining always more exaggerated in the eye in which it first appeared, the recession of the eyeball occurring in the reverse order. This condition is also shown in photographic illustrations (Figs. 41 and 42).

In a small number of our cases there developed on the resumption of activities symptoms of hypothyroidism, the basal metabolic rates ranging from −15 to −30. Hypothyroidism of this kind is usually only relative, and is induced

by a rapid gain in weight and a return to physical activity before the gland residue has resumed its full function. In all except 8 cases normal metabolism was restored within six months by the administration of small doses of thyroid extract, which was discontinued as soon as the basal rate and pulse rate had become stabilized at a normal level. It is probable that in some of these cases the adjustment of function upon a normal basis was the result of glandular

Fig. 42.—Same patient as in Fig. 41, three months after operation, showing absence of all eye signs except slight widening of right palpebral fissure.

hypertrophy—a controlled hypertrophy limited to body requirements.

In 8 cases it has been necessary to continue the use of thyroid extract indefinitely. Oddly enough these are not the cases in which the most radical procedures were carried out. One may be justified in assuming that the function of the gland residue has been diminished by postoperative vascular thrombosis or a progressive fibrosis. In none of the cases has the deficiency been complete. In none has it been neces-

sary to administer more than 2 grains of whole gland preparation daily, and, in contrast to the loss of weight which follows complete glandular removal or destruction, body weight has been maintained at the maximum.

Smith and his associates have found that postoperative myxedema is especially likely to develop in those cases in which the microscopic examination shows the presence of a large number of acidophilic cells in the tissue removed.

In none of our operative cases, either of the Graves' or the adenomatous type, has postoperative tetany been sufficiently marked to be diagnosed objectively. Two patients complained temporarily of stiffness of the hands in the morning, with difficulty in unfolding the fingers. In neither was the calcium content of the blood found to be below normal. In a series of observations Rabinowitch found a reduction in the blood calcium following thyroidectomy, the reduction varying directly with the extent of gland removal. In all cases, however, there was a return to normal within a period of nine days.

In one of our cases of Graves' disease the right recurrent laryngeal nerve was injured. Following operation phonation was very defective, but by the end of a year the presence of abductor paralysis could be detected only on laryngoscopic examination. Compensatory movement of the companion cord was so perfect that the patient was able to resume her singing in a choir without impairment of pitch or volume. In the operative treatment of 1050 cases, including both Graves' and adenomatous disease, there has been no instance of bilateral nerve injury.

GRAVES' DISEASE WITH ADENOMA.

In 22 of our cases of Graves' disease (6.5 per cent) there was found at operation or upon section of the gland an associated adenoma or adenomata. In none was the

presence of the adenoma positively diagnosed prior to operation, but in cases which are persistently refractory to iodine we have come to suspect associated adenomatous disease. The following is a report of one of these cases:

Case Report No. 9.

Female, aged forty years, widow. Admitted December 10, 1924.

Present Illness: Severe influenza in 1918, followed immediately by thyroid enlargement and symptoms of dysfunction.

Condition on Admission: Full Graves' syndrome of severe type. Diarrhea, restlessness, marked tremor of hands and lips, well-marked ocular signs. Pulse, 140. Basal metabolic rate, +70. There was generalized smooth enlargement of the thyroid.

Preoperative Course: The administration of iodine, although relieving the extreme restlessness and apprehension and largely abolishing the stare, failed to affect the basal metabolism in a commensurate degree. For this reason it was suspected that the case was of the mixed type and that activation of the associated adenoma or adenomata was responsible for the persistently high rate.

Operation: February 11, 1925, under gas-oxygen and local infiltration, right lobectomy. On gross section of the lobe there was found a rapidly-growing adenoma, $1\frac{1}{2}$ cm. in diameter. On March 6, the left lobe and isthmus removed. Uneventful recovery.

Postoperative Course: Since operation the patient has been free from symptoms.

The course of this and similar cases lends support to our present practice of withholding iodine, or prescribing it in minimal doses only, in all cases of adenomatous disease, whether toxic or quiescent, until patients are in hospital and its effects can be checked by frequent metabolism tests.

Clinical Tables.

Total number of cases	334
Number of male patients	57
Number of female patients, of whom 60 per cent were married	277
Previous adolescent goiter with subsidence, 18 cases	5.4 per cent
History of goiter in other members of family, 77 cases	23.0 per cent
Jewish patients, 41	12.0 per cent
Age at which goiter appeared, average	30.6 years
Age at which symptoms appeared, average	31.7 years
Age on admission, average	32.0 years
Previous roentgen-ray treatment, 18 cases	5.4 per cent
Previous radium treatment, 5 cases	1.5 per cent

Table of Symptoms.

	Per cent.
Undernourished	46.0
Appetite:	
Increased	37.0
Decreased	15.0
Normal	41.0
Variable	7.0
Diarrhea	18.0
Vomiting	16.0
Dyspnea on exertion	67 0
Sweating	62.0
Flushing of face and neck	51.0
Fugitive erythema of face and neck	31.0
Tremor of hand	94.0
Palpitation	86.0
Precordial thumping	73.0
Nervousness	94.0
Restlessness (fidgetiness)	68.0
Irritability	59.0
Heat intolerance	69 0
Edema of ankles	29 0
Falling of hair	35.0
Loss of weight, average 15 pounds	
Loss of strength	78.0
Quadriceps weakness	61.0
Exophthalmos	56.0
No exophthalmos, but definite eye signs	21.0
Pulsation in gland	64.0
Thrill	18.0
Bruit	67.0
Diabetes, 3 cases	9.0
Pulse on admission, average	115
Systolic pressure, average	112
Diastolic pressure, average	77
Pulse pressure, average	65

	Per cent.
Cardiac arrhythmia, 19 cases	5.7
Cardiac murmurs (majority functional)	60.0
First untreated basal metabolic rate, average	+47
Basal metabolic rate immediately before operation, average	+32
Preoperative rest:	
1921–1923, average number days (No iodine treatment)	21
1924–1927, average number days (Iodine treatment)	13.7

Operations.	Per cent.
Ligation, 29 cases	8.6
Deaths following ligation, 2 (Case reports No. 11 and No. 19)	
Average drop in basal metabolic rate after ligation	7.0
Separate lobectomies, 24 cases	7.1
Deaths following lobectomy, 2 (Case reports No. 20 and No. 22)	
Average drop in basal metabolic rate after first lobectomy	11.0
One-stage subtotal thyroidectomy, 309	92.5
Deaths following one-stage radical operation, 10	3.0
Total deaths, 14	4.1

Results of Treatment.	Per cent.
Cured (including 8 cases with slight hypothyroidism), 312	93.4
Slight residual dysthyroidism, but no subjective symptoms, all patients working steadily, 8	2.5
Effect of operation on ocular signs:	
Cured	57.0
Improved	35.0
Not improved	8.0

Analysis of the Eight Cases of Hypothyroidism.

Basal metabolic rate maintained within normal limits with whole gland preparation, 2 grains daily	1
Basal metabolic rate maintained within normal limits with whole gland preparation, 1 grain daily	6
Basal metabolic rate maintained within normal limits with whole gland preparation, 1 grain every second day	1

Analysis of Postoperative Deaths.	Cases.
Sudden death on table	2
No. 10. Adrenalin, status lymphaticus, cardiac	
No. 14. Adrenalin, cardiac	
Bronchopneumonia—Nos. 11, 16, 21	3
Cardiac dilatation—Nos. 12, 17, 18, 20	4
Unexpected death on fourth day postoperative after smooth recovery from operation, from either acute dilatation, bronchopneumonia, or cerebral hemorrhage. No autopsy. No. 23	1
Mesenteric embolism five days eight hours postoperative. No. 13	1
Streptococcus wound infection. Septicemia. No. 15	1
Postoperative thyroid crisis. No. 19	1
Acute nephritis. Myocarditis. No. 22	1
	14

	Cases.
Operations:	
Bilateral resections with isthmus (Nos. 12, 13, 15, 16, 17, 18, 21, 23)	8
Unilateral ligation (Nos. 11 and 19)	2
Right lobectomy (Nos. 20 and 22)	2
On table following injection of neck with novocain and adrenalin (Nos. 10 and 14)	2
	14
Pallor:	
A marked clinical feature in	6
Cardiograms:	
No cardiogram. No clinical evidence of fibrillation (Nos. 10, 14, 19)	3
Cardiogram normal (Nos. 11, 12, 13, 16, 21) No. 13 developed auricular fibrillation clinically after operation and died from mesenteric embolism.	5
Left ventricular preponderance (Nos. 15, 17, 23)	3
Inversion of *T* (Nos. 18 and 20)	2
Auricular fibrillation. (No. 22)	1
	14

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Case Reports of Patients Who Died after Operation for Graves' Disease.

Case Report No. 10.

Male, aged forty-four years. Mechanical engineer.
Admitted: June 25, 1921.

Present Illness: Attack of quinsy in December, 1919. Present symptoms developed March 1, 1921. Rapid loss of weight, 50 pounds. Tremor. Weakness.

Condition on Admission: Full Graves' syndrome. Pronounced stare; Graefe and Stellwag signs; glistening cornea; no exophthalmos. Apprehensive. Tremor of hands and lips. Emotional. Frequent crying spells. Diarrhea two or three days a week. Appetite increased. Marked heat intolerance. Moderate grade of generalized enlargement of thyroid, with pulsation and bruit. Transverse cardiac dulness, 9 cm. No murmur. Pulse range, 112 to 140.

Treatment: Absolute rest in bed; isolation; hand feeding; ice-packs; and sedatives. (No iodine.)

Preoperative Basal Metabolic Rate and Pulse: June 26, basal metabolic rate, +81; pulse, 130; July 1, basal metabolic rate, +61; pulse, 118; July 13, basal metabolic rate, +68; pulse, 108; July 16, basal metabolic rate, +52; pulse, 96.

Operation: July 18, bipolar ligation. Mild reaction. Subsequently marked general improvement.

Basal Metabolic Rate and Pulse After Ligation: July 25, basal metabolic rate, +66; pulse, 120; August 7, basal metabolic rate, +62; pulse, 112; August 18, basal metabolic rate, +57; pulse, 100; August 30, basal metabolic rate, +52; pulse, 96; September 6, basal metabolic rate, +43; pulse, 88.

Operation September 8: Prepared for thyroidectomy. Injection of left half of line of skin incision with novocain and adrenalin had just been completed when patient gave a slight cry. The pupils were dilated, the face ashen, pulse not obtainable in neck. No further respiratory movements. Artificial respiration without effect.

Autopsy: Adenoid goiter (Graves'). Hypertrophy of thymus. Hyperplasia of lingual, tonsillar, and pharyngeal lymphoid tissues. Dilatation of right side of heart, especially auricle (acute). Edema of pia-arachnoid (acute). Mild chronic nephritis. Chronic ethmoiditis.

Case Report No. 11.

Female, aged twenty-four years.

Admitted: March 6, 1923.

Present Illness: Goiter developed at fourteen. Symptoms appeared shortly afterward and persisted— nervousness, tremor of hands, palpitation and prominence of eyes. No prolonged rest. Periods of improvement alternating with exacerbations.

Special Clinical Features: Very large, firm, generalized enlargement of thyroid. Marked exophthalmos. Very apprehensive. Pulse 136, regular. Transverse cardiac dulness, $13\frac{1}{2}$ cm. Systolic bruit over pulmonary area. Blowing systolic over aortic area (no diastolic bruit heard). Moderate myocardial disease probably no aortic valvular defect. Blood pressure, 175/95. Cardiogram, normal. Urine, normal. Throat, enlargement of lingual tonsil. No focus of infection found. Basal metabolic rate, +56.

Treatment: Absolute rest in bed; isolation; ice-bags. (No iodine.) After a week's rest pulse range 80 to 120.

Operation: March 13, under local anesthetic, right polar ligation, performed in bed. Slight reaction. Improvement. Patient more confident, and anxious for second ligation.

Operation: March 20, under local anesthetic, left polar ligation, in bed. Patient irritable during operation and pulse up to 160. Expression not good.

Five hours postoperative complained of severe pain in right axilla. Respiration, 28; temperature, 99.6° F.; pulse, 148. Twenty-four hours postoperative, right bronchopneumonia. Respiration, 36. Maximum temperature, 100.8° F. Pulse by stethoscope rose to 214, falling later to 136 to 156. Patient restless and delirious. Died forty-four hours postoperative.

Cause of Death: Bronchopneumonia.

No autopsy.

Case Report No. 12.

Female, aged twenty-eight years. Housewife.

Admitted: February 20, 1922.

Diagnosis: Graves' disease.

Family History: Mother has goiter. Grandmother died of goiter.

Present Illness: At seventeen had palpitation when nursing sick sister. Subsequently well. Two years ago badly frightened when alone in her home. Has since had palpitation. In February, 1921, home destroyed by fire, a severe shock. Tremor dates from this event. Goiter first noticed February, 1921.

Clinical Features: Pallor; loss of 30 pounds in weight; recurring attacks of diarrhea; vomiting; sweating; restlessness and irritability; insomnia; exophthalmos; marked firm generalized enlargement of thyroid with pulsation and bruit. Transverse cardiac dulness, 10 cm. Pulse, 120 to 140. Blood pressure, 122/56. Edema of ankles. Cardiogram, normal.

Treatment: Rest. Digitalis. (No iodine.)

Preoperative Basal Metabolic Rate and Pulse: February 21, basal metabolic rate, +41; pulse, 130; February 27, basal metabolic rate, +52; pulse, 120; March 6, basal metabolic rate, +29; pulse, 108.

Operation in room, March 8, subtotal thyroidectomy. Anesthetic -gas-oxygen, 0.5 per cent novocain with adrenalin for skin incision, 0.5 per cent novocain for deep injections. Pulse during operation, 130 to 140.

Postoperative Course: Condition good until 1 A.M. on 9th when pulse became rapid and thready. Improved after intravenous glucose saline. At 8 A.M. condition much improved. Mind clear at all times. Not restless. Temperature, 99° F. At 10 A.M. temperature, 102.6° F. Pulse very rapid. At 10.30 A.M. died suddenly, twenty-four hours postoperative. Cardiac dilatation. No autopsy.

Case Report No. 13.

Female, aged thirty-four years. Trained nurse.

Admitted: August 31, 1923.

Diagnosis: Graves' disease.

Present Illness: Symptoms developed April, 1921. Nervousness, palpitation, headaches. Improved after rest. After nine months' care of insane patient symptoms recurred March, 1923; much more severe. Pulse, 170. Since confined

to bed, under bromides, quinine hydrobrom., and tincture of iodine, 15 ♏ t.i.d. Goiter first noticed March, 1923.

Condition on Admission: Large, uniform, soft enlargement of thyroid. Nutrition poor. Very pronounced tremor. Pale. Severe headaches. Marked heat intolerance. Exophthalmos; Graefe, Stellwag and Joffroy signs. Pulsation, thrill, and bruit over gland. Transverse cardiac dulness, 12 cm. Diastolic shock, loud basal systolic. Pulse, 120. Blood pressure, 190/80. Cardiogram, normal. Edema of ankles. Red blood cells, 4,280,000. Hemoglobin, 70 per cent.

September 1, basal metabolic rate, +88; pulse, 114; September 11, basal metabolic rate, +85; pulse, 106. September 15, developed attack of tonsillitis. Temperature, 103.6° F.; pulse, 130. Afebrile by September 22.

October 1, basal metabolic rate, +24. Discharged. To remain at rest under Lugol's solution, 3 ♏ t.i.d. To return later for operation.

Readmitted November 4: At rest in bed during interval. Much calmer. Gain of 24 pounds in weight.

Preoperative Basal Metabolic Rate and Pulse: November 6, basal metabolic rate, +20; pulse, 96; November 13, basal metabolic rate, +11; pulse, 84.

Operation: November 16, subtotal thyroidectomy under gas-oxygen, with infiltration of skin with novocain and adrenalin. Pulse throughout operation, 100.

Postoperative Course: Moderate febrile reaction. Maximum temperature, 100.4° F., but pulse at times irregular, fibrillation. Pulse range, 136 to 144.

November 19, at 10.45 P.M., eighty-two hours postoperative, complained of severe abdominal pain passing through to back, with nausea. Enema very effectual, but pain continued. Later vomited and became very restless. Morphia gave some relief.

November 20, at 2 A.M., recurrence of severe pain radiating over whole abdomen, especially severe in back. Vomited brownish material. Second enema not effectual. Severe recurrences of pain at 4.30 A.M. and 7 A.M. Rectal temperature, 97.4° F. At 10 A.M. marked abdominal facies. No dis-

tention. No rigidity. No fluid in flanks. No tumor. Volvulus, intussusception, perforated gastric or duodenal ulcer, hernia, and strangulated Meckel's diverticulum, were in turn considered and dismissed as improbable. In view of long-standing cardiac trouble, and the occurrence after operation of auricular fibrillation coupled with sudden and severe pain in umbilical region referred to the back, mesenteric embolism thought most likely cause of symptoms.

Operation: Under gas-oxygen-ether anesthesia, abdomen opened in median line below umbilicus. Slate-colored small bowel presented. No pulsation in mesentery. Area of discoloration began about 6 inches above ileo-cecal valve and extended upward along the bowel for a distance of 12 feet. Resection; end-to-end anastomosis.

Death: Thirty hours postoperative.

Pathological Report on Specimen: Thrombosis, mesenteric arteries.

No autopsy.

Case Report No. 14.

Female, aged fifty-eight years. Syrian.

Admitted: February 2, 1924.

Diagnosis: Graves' disease.

Present Illness: Impossible to secure satisfactory history. Enlargement of thyroid present for indefinite period. Two months' rest in bed prior to admission. Symptoms of nervousness, tremor, and palpitation for several months.

Condition on Admission: Moderate grade of generalized enlargement of gland. Pronounced eye signs, but no exophthalmos. Patient pale, emotional, and very apprehensive. Pulse, 120; extra systoles. Cardiac impulse diffuse. Transverse cardiac dulness, 10 cm. Faint presystolic thrill. Blood pressure, 135/85. Urine: albumin +, no casts. Urea nitrogen, 14. Creatinine, 1.02. Urea concentration factor, 29. Blood sugar, 0.125. Basal metabolic rate, +3.

Treatment: Rest in bed. Lugol's solution, 3 ℳ t.i.d.

Preoperative Basal Metabolic Rate and Pulse: February 8, basal metabolic rate, +17; pulse, 110; February 19, basal metabolic rate, +31; pulse, 96; February 26, basal metabolic

rate, +17; pulse, 92; March 4, basal metabolic rate, +2; pulse, 88.

March 20, prepared for operation. Local anesthetic, novocain with adrenalin. Patient tranquil; pulse, 110 to 120. Operation had proceeded to stage where prethyroid muscles divided and gland exposed when suddenly heart action and respiration ceased. Following artificial respiration and oxygen inhalations there were two or three slight respiratory movements, but no return of heart sounds. Death precisely similar to Nos. 10 and 30.

Autopsy (except head): Thyroid lobes 3 inches by 1½ inches. Adenoid goiter. No adenomata. Heart, 390 gm. No gross lesion. Adrenals negative. Other organs normal for age.

Case Report No. 15.

Female, aged forty-five years.

Admitted: March 30, 1925.

Diagnosis: Graves' disease.

Present Illness: Goiter present for seven years. Recession and then increase in size. Symptoms present for two and a half months.

Clinical Features: No eye signs. Obese, 183 pounds on March 13. Marked hypertension, 212/60. Moderate grade of generalized enlargement of thyroid. Urine: specific gravity, 1.010; no albumin. Cardiogram, left ventricular preponderance.

Preoperative Basal Metabolic Rate and Pulse: Refractory to iodine. While at rest in bed basal metabolic rate declined from +72 on March 13 to +46 on April 17, then gradually rose to +66 on April 29, finally falling to +37 on May 16, four days before operation. Pulse range for the week before operation, 84 to 96. Weight, 160 pounds.

Operation: May 20, under local anesthesia (novocain), subtotal thyroidectomy. Pulse throughout 120 to 130.

Postoperative Complications: Wound infection (streptococcus), cellulitis of neck, reaching height on fourth day postoperative with temperature of 104° F. On fifth, sixth and seventh days postoperative temperature ranged from

98° to 100.6° F., with improvement in general condition. On afternoon of eighth day postoperative temperature rose suddenly from 98° to 102° F., with development of pulmonary signs. On ninth day postoperative temperature reached 104-8° F., and before death at 6 A.M. on eleventh day postoperative, 107.8° F. No autopsy.

Cause of Death: Streptococcus wound infection. Streptococcus septicemia. Streptococcus pneumonia.

Case Report No. 16.

Male, aged seventeen years.

Admitted: May 24, 1925.

Diagnosis: Graves' disease.

Present Illness: Goiter present for one and a half years, adolescent passing into adenoid. Duration of symptoms, nine months.

Special Clinical Features: Very large uniform swelling of both lobes and isthmus. No eye signs. Persistently rapid pulse. Cardiogram negative.

Preoperative Basal Metabolic Rate and Pulse: Under rest and iodine, basal metabolic rate rose from +53 on May 16 to +66 on June 9, and then on June 22, four days before operation, declined to +39. Pulse on day before operation 116 to 128.

Operation: June 26, under local anesthesia (novocain), bilateral partial lobectomy. Pulse throughout, 90 to 120.

Postoperative Complications: Bilateral pneumonia.

Died: Forty-eight hours postoperative.

Autopsy: Areas of consolidation in right apex and consolidation of right lower lobe. Areas of consolidation in left apex and consolidation of left lower lobe. Dilatation of right side of heart. Congestion of kidneys. Fatty liver. Bacteriological examination of pulmonary exudate, B. mucosus capsulatus (Group III pneumococcus).

Case Report No. 17.

Female, aged twenty-eight years. School teacher.

Admitted: May 9, 1925.

Diagnosis: Graves' disease.

Present Illness: No enlargement of thyroid noticed. Symptoms of nervousness and palpitation for four years. No loss of weight.

Clinical Features: Pallor, sweating, tremor of hand, insomnia. No eye signs. Pulse, 100, regular. Transverse cardiac dulness, 11 cm. Systolic murmur at apex, not transmitted. Blood pressure, 120/80. Cardiogram normal. May 11, basal metabolic rate, +12; May 16, basal metabolic rate, +5.

May 19, discharged on advice of physician. To rest in bed. Lugol's solution, 2 ♏ t.i.d.

Readmitted: October 7. No improvement. Pulse, 90. Transverse cardiac dulness, 13 cm. Soft systolic bruit 4th i.s. Blood pressure, 140/80. Cardiogram, auricular extra systoles: the type of Q.R.S. group tending toward that seen in left ventricular preponderance, there being an alteration in this regard since May. Urine, faint trace sugar. Urea nitrogen, 15. Creatinine, 1.22. Urea concentration factor, 37. Basal metabolic rate, −5. Because of beginning myocardial changes operation advised. Pulse range day before operation, 88 to 120.

Operation: October 13, under local anesthesia (novocain), bilateral partial lobectomy. Very slight enlargement of gland. One-half of each lobe together with isthmus removed. Pulse during operation, 100 to 110.

Postoperative Course: A fairly good night following operation. Seen at 9.30 A.M. on 14th. Temperature, 100° F.; pulse, 100. No complaints. At 10 A.M. usual pallor became more marked. Died suddenly at 10.30 A.M., twenty-four hours postoperative. Cardiac death. No autopsy.

Case Report No. 18.

Male, aged forty-three years. Accountant.

Admitted: July 19, 1925.

Diagnosis: Graves' disease.

Present Illness: Goiter since November, 1923. Symptoms including exophthalmos since November, 1923.

Condition on Admission: Full Graves' syndrome. Marked pallor. Delusions of persecution at times. Emaciated. Extremely weak. Exophthalmos marked. Marked generalized enlargement of thyroid with pulsation, thrill, and bruit. Consistence firm. T.C.D., 3/15.5 cm. Systolic murmur over whole precordium. Pulse, 112 to 140, regular. Blood pressure, 136/54. Cardiogram: inversion of *T* in Leads 2 and 3. Urinalysis: trace of albumin at times. No casts.

Treatment: Rest in bed. Isolation. Lugol's solution.

Preoperative Basal Metabolic Rate and Pulse: Basal metabolic rate declined from +50 on admission to +8 on August 8, and pulse to 90. Operation advised, but refused. On September 18, basal metabolic rate, +87, at height of relapse. On November 11, basal metabolic rate, +26; pulse, 84.

Operation: November 17, 1925, subtotal thyroidectomy, under local anesthetic (novocain). Pulse during operation, 120 to 140.

Postoperative Course: Maximum temperature, 100.4° F. Pulse 130, rising to 160; regular, good volume. Became cyanosed at 11 P.M., November 18, and died at midnight, thirty-eight hours postoperative, probably from acute cardiac dilatation.

No autopsy.

Pathological Report: Adenoid goiter, with benign adult adenoma also showing adenoid heterotrophy.

Case Report No. 19.

Female, aged twenty-two years. Stenographer.

Admitted: December 31, 1925.

Diagnosis: Graves' disease.

Present Illness: Enlargement of neck present for six months. Symptoms present for eight months.

Clinical Features: Face pale. Marked tremor of hands. Marked heat intolerance. Restlessness. Loss of 36 pounds in weight. Exophthalmos. Graefe. Stellwag. Marked generalized enlargement of thyroid with pulsation, thrill, and loud bruit. Pulse 140, regular. Apex beat 5th i.s., a.a. line. Heaving impulse. Systolic murmur over whole precordium. Blood pressure, 165/70.

Treatment: Lugol's, 5 ♏ t.i.d., increased to 20 ♏ t.i.d. Bromides. Isolation. Ice-packs.

Preoperative Basal Metabolic Rate: January 7, 1926, basal metabolic rate, +64; January 11, +81; January 15, +68; January 19, +46; January 23, +36.

Cardiogram not taken because of excitability of patient. Pulse range the day before operation, 120 to 130.

Operation: January 29, under gas-oxygen anesthesia, right polar ligation (in bed). Time, six minutes. Pulse throughout, 160 to 130 to 180.

Postoperative Course: Crisis. Restlessness and delirium. Pulse range forty-eight hours postoperative, 190 to 120, rising then to 200 with dilatation of heart. Maximum temperature, 100.4° F.

Death: Sixty-nine hours postoperative.

No autopsy.

Case Report No. 20.

Male, aged fifty-six years. Farmer.

Admitted: January 11, 1926.

Diagnosis: Graves' disease.

Present Illness: Goiter developed in 1919, following influenza. Symptoms began at same time. Gave up work for about two years, but continued to get worse. Bilateral polar ligation at Mayo Clinic, 1921; marked improvement, and until autumn of 1925 able to do work as usual. In September, 1925, became very nervous and short of breath. Lost weight. Diarrhea at times. Lugol's solution, 10 ♏ daily, since autumn.

Present Condition: Poorly nourished. Irritable. Expression anxious and tense. Loss of 30 pounds in past three months. Full Graves' syndrome with exophthalmos. Gland very prominent, lobes extending above into submaxillary triangles and below to sternoclavicular joints; very hard. Loud bruit over whole gland. T.C.D., 13 cm. Heaving impulse. No murmur. Irregular. Pulse, 100; small. Blood pressure, 165/90. Cardiogram: inversion of *T* in all leads; auricular fibrillation. Urinalysis: faint trace of albumin; no casts.

Preoperative Basal Metabolic Rate and Pulse: January 19, basal metabolic rate, +70; pulse, 96. January 23, basal metabolic rate, +77; pulse, 90. January 27, basal metabolic rate, +69; pulse, 96.

Treatment: Absolute rest. Hand feeding. Lugol's. Bromides. Digitalis. Ice-packs.

Operation: January 30, under local anesthesia (novocain), right lobectomy. Pulse throughout, 96.

Postoperative Course: Maximum temperature, 100.4° F.; pulse, 118. In good condition until midnight 31st. Died at 2.30 A.M. February 1, forty hours postoperative. Cardiac failure.

Autopsy: Hypertrophy of left ventricle. Dilatation right side of heart (acute). Hypostatic congestion and marked edema both lower lobes. Atrophic nodular liver.

Case Report No. 21.

Female, aged twenty years.

Admitted: August 3, 1927.

Diagnosis: Graves' disease.

Present Illness: Generalized enlargement of thyroid for two years. Nervousness and palpitation for same period. Amenorrhea for three months.

Condition on Admission: Gland prominent and firm. Bruit over right lobe only. T.C.D., 9 cm. No murmurs. Pulse, 130; regular. Cardiogram normal; rate, 160.

Treatment: Rest in bed. Lugol's solution, 5 ♏ t.i.d.

Preoperative Basal Metabolic Rate and Pulse: August 3, basal metabolic rate, +46. August 9, basal metabolic rate, +36; pulse, 120. August 13, basal metabolic rate, +24; pulse, 124.

Operation: August 18, subtotal thyroidectomy under local anesthetic (novocain).

Postoperative Course: On the day following operation the temperature rose from normal in morning to 104.8° F. at midnight. Pulse from 130 to uncountable rate. Respirations from 22 to 40. On second day postoperative temperature gradually declined to 99.6° F. and respirations to 36, but pulse remained uncountable.

Death: Fifty-six hours postoperative.
Autopsy: Bilateral bronchopneumonia.

Case Report No. 22.

Female, aged forty-two years. Housewife.
Admitted: February 17, 1927.
Diagnosis: Graves' disease.
Present Illness: Goiter since thirteen years of age. Symptoms present for six years. Exophthalmos for five years. Radium treatments in 1923-1924 without improvement. Bed-rest for three months in 1925, with temporary improvement. During past year condition worse. Appetite increased.
Condition on Admission: Poorly nourished. Full Graves' syndrome. T.C.D., 14 cm. Heart action grossly irregular. Pulse, 96 to 106. No pulse deficit. Blood pressure, 140/80. Edema of ankles. Basal metabolic rate, +50. Cardiogram: auricular fibrillation; right auricular extra systoles. Urinalysis: 1.014, albumin ++, blood disks, many epithelial, granular and hyalin casts.
Treatment: Low-protein diet. Digitalis. Lugol's solution.
Preoperative Basal Metabolic Rate and Pulse: February 17, basal metabolic rate, +50. February 22, basal metabolic rate, +32; pulse, 96. February 28, basal metabolic rate, +18; pulse, 76. March 4, basal metabolic rate, +16; pulse, 76. March 15, basal metabolic rate, +22; pulse, 72.
Operation: March 21, under local anesthetic (novocain), right lobectomy and removal of isthmus. Condition good throughout. Pulse, 78.
Postoperative Course: No crisis. Developed acute exacerbation of old parenchymatous nephritis. Urine loaded with albumin; blood casts. Subfebrile temperature. Pulse, 76 to 80. Complained of headache, nausea, and backache. Later became drowsy. Wound normal. On sixth day postoperative, much improved. Blood casts and blood in urine began to clear up, but albumin remained about the same.
Death: Died suddenly forenoon March 30, after "a very good night," nine full days postoperative.

Cause of Death: Acute nephritis. Myocarditis.
No autopsy.

CASE REPORT NO. 23.

Female, aged sixty-three years.
Admitted: February 13, 1927.
Diagnosis: Graves' disease.
Past History: Mother of nine children. Husband died one year ago after illness of one and a half years, during which time patient was under constant strain.
Present Illness: Goiter since adolescence; increase in size one year ago. Symptoms of thyrotoxicosis developed in April, 1926; very acute. Loss of 50 pounds in a few weeks. Extreme weakness, palpitation, tremor. After several weeks improved, with gain in weight, but unable to do housework. Confined to bed for past month.
Present Condition: Poorly nourished. Expression anxious. Full Graves' syndrome including exophthalmos. Atrophic changes in finger nails. Gland large, irregular in outline, but not suggestive of adenoma; consistence firm. Bruit over both lobes. T.C.D., 12 cm. Heaving impulse. Short systolic murmur, maximum in mitral area. Pulse, 98; regular. Blood pressure, 140/60. Cardiogram: left preponderance; inversion of *T* in Leads 2 and 3. Urine normal.
Treatment: Rest. Lugol's solution.
Preoperative Basal Metabolic Rate and Pulse: February 14, basal metabolic rate, +91; pulse, 108. February 18, basal metabolic rate, +65; pulse, 90. February 22, basal metabolic rate, +40; pulse, 84. February 25, basal metabolic rate, +34; pulse, 80.
Operation: February 28, subtotal thyroidectomy, under local anesthetic (novocain). Pulse throughout, under 100.
Postoperative Course: Early postoperative course unusually smooth. Pulse range, 100 to 110, falling to 82 on third day. Temperature range, normal to 100° F., rising to 102.6° F. at 8 P.M. on third day. Pulse, 96. Respiration, 22.
Death: Died suddenly at 2 A.M. March 4, eighty-six hours postoperative.
Cause of Death: Bronchopneumonia; acute cardiac dilatation?
No autopsy.

CHAPTER X.

IODINE THYROTOXICOSIS.

Iodine thyrotoxicosis is initiated in cases of adolescent goiter or non-toxic adenoma by excessive iodine medication. The publicity which in recent years has been given to iodine as a remedy for goiter and the numerous patent medicines on the market have been responsible for many cases of iodine thyrotoxicosis. In our own clinic, cases have developed because iodine was taken in excess of the dosage prescribed or prescriptions were renewed from time to time outside the hospital without instruction from the clinic.

We deal in Chapter XI with the effect of iodine on adenomatous disease.

Iodine intoxication occurring in cases of adolescent goiter closely simulates Graves' disease. Tachycardia, tremor, loss of weight, and elevation of the basal metabolism are the four cardinal symptoms. Eye signs are absent. The appetite is diminished.

With rest amid quiet surroundings many of these patients gradually regain a normal physiological balance, but there are others in whom this balance can be restored only by removal of the greater part of the gland.

The following case report will best illustrate the cardinal points of this type of thyroid intoxication.

Case Report No. 24.

Female, aged fourteen years and six months, milliner's assistant. Seen in clinic September 26, 1923, complaining of swelling of neck, present for three months.

Past History: Menstruation established four months ago.

Examination: Prominent bilateral enlargement of thyroid, consistence soft. No murmur over gland. Circumference of neck, 38 cm. Pulse normal—84. No tremor of hand. No ocular signs. Weight, 119 pounds.

Diagnosis: Juvenile goiter.

Treatment: Ten hours rest in bed nightly; fresh green food; sea fish; sodium iodide.

On December 18 weight, 124; circumference of neck, 35 cm. Instructed to report in two months. Patient did not, however, report until June 9, 1924. Had been taking iodine continuously since last visit, contrary to instructions. Had to give up work two weeks ago. Loss of 25 pounds in past five weeks. Weight, 98. Pulse, 140. Circumference of neck, 32 cm. Basal metabolic rate, +52. Marked tremor of hand. No ocular signs.

Diagnosis: Iodine thyrotoxicosis. To rest in bed at home. On July 9 weight 95; no improvement. Admitted to hospital for observation on July 19.

	Basal metabolic rate.	Pulse.	Weight.
July 22	+31	132	87
August 9	+15	130	87
August 26	+13	132	91½
September 13	+17	130	101
September 30	+17	120	110
October 6	+12	120	112
October 11	+12	120	113
October 17	+ 6	116	113½
October 23	+ 9	116	115

During this period of three months' observation in hospital, Lugol's solution in doses varying from 1 ♏ every second day to 5 ♏ twice daily was given, without evident amelioration of the symptoms. The effect of prolonged strain upon the myocardium was feared, and on consultation it was decided that operation offered the best prospect of early and permanent recovery.

Operation: October 28, under local anesthesia, subtotal thyroidectomy. Recovery uneventful.

Pathological Diagnosis: Hyperplasia, with diffuse intra-acinar epithelial growth (iodine toxicity).

November 8, basal metabolic rate, −1; pulse, 88; weight, 114.

February 3, 1926: Fifteen months after operation, basal metabolism, normal; pulse, 76; weight, 127. No complaints. No symptoms. Working steadily for past six months.

CHAPTER XI.

ADENOMATOUS DISEASE NON TOXIC.

Adenomatous disease occurs in precisely the same districts or goitrous belts as does juvenile goiter, that is, in regions in which there is a shortage of iodine in food and water. I am inclined to believe, however, that there is more than the simple relationship of locality between the two conditions. Adenomatous disease usually develops later in life, and a history of juvenile goiter is given so frequently in these cases that it seems reasonable to assume that the adenomata had their beginnings in the functional derangement of the thyroid at that time. Even if, as is often stated, the earlier enlargement disappeared long before the adenomata were noticed, it is probable that changes initiated in the gland at that time persisted in some form, though not clinically evident. In still other instances adolescent disease has progressed without intermission into the nodular type. And, in those cases of adenomatous disease in which juvenile goiter is not recorded, it is possible that it was present, though not sufficiently pronounced to be evident to the patient or remembered by him.

Adenomata are sometimes single, more often multiple, and usually bilateral. They range in size from the microscopic nodule to the large, single or multiple, globular masses which extend from the submaxillary triangle to the upper aperture of the thorax and laterally encroach upon the posterior triangles, with displacement of the great vessels. As a rule they progress slowly.

The consistence may be soft, firm, elastic (cystic), or hard (calcified), depending upon the kind and extent of the secondary degenerative change, and it may vary in different nodules in the same gland.

There may be no symptoms. On the other hand, toxic symptoms or pressure upon the trachea may develop.

In unilateral growths the degree of tracheal and even laryngeal displacement may be fantastic, but it is not always in these cases that pressure signs are greatest, although in unilateral growths of large size difficulty in breathing is a common complaint. Bilateral tumors tend to decrease the transverse diameter of the trachea. In exaggerated cases there is actual stenosis. It is in cases of this kind that one is most likely to wound the projecting scabbard-shaped trachea in performing resection.

The size of the palpable tumor is not a reliable gauge of the imminence of pressure symptoms. Comparatively small tumors springing from the anterior margins of the lobes or developing in the isthmus may be the cause of a rapidly developing tracheal compression. Should hemorrhage occur into a tumor so placed, sudden death from suffocation may occur. It is in the antero-posterior plane rather than in the lateral plane that the trachea is most susceptible to compression.

The mechanism of compression varies. For example, in a large left-sided tumor the patient may complain of respiratory distress when lying on the left side, due to the stretching and further narrowing of the trachea coincident with the altered relation between the head and the left shoulder, the weight of the head on the soft pillow making more acute the angle between the neck and the shoulder on that side. Other patients with a similarly placed tumor may complain of respiratory distress when lying upon the right side, due to the fact that that part of the weight of the tumor which is supported by the clavicle when the head is held in the upright position is transferred to the trachea. In cases where the lower portion of the tumor is engaged in the upper opening of the chest, tracheal compression may occur only when the individual bows his head or stoops forward.

In many cases of tracheal compression the encroachment

upon the airway is so gradual that patients are not aware of any respiratory disability. At the most they will admit that they are short of breath on exertion, but this is usually attributed by them to obesity or advancing years. Chronic tracheal compression throws added work upon the heart muscle and to this can be traced the development of myocardial changes in patients whose basal metabolism has remained normal and who are apparently free from thyrotoxicosis. We have had several of these cases in the clinic. The following case report is illustrative:

Case Report No. 25.

Clergyman, aged fifty-eight years. Admitted January 10, 1923.

Complaints: Feeling of pressure in neck; severe congestive headaches; irregular heart action.

Present Illness: Enlargement of neck since age of twenty. Gradual increase in size. Headaches for past six years. No symptoms of hyperthyroidism at any time. Appetite good. Weight steady. No loss of strength.

Present Condition: Very prominent globular mass, 9 by 12 cm., springing from left lobe of thyroid. No pulsation or bruit. No ocular signs. No tremor. Roentgen-ray showed marked displacement of trachea to right, with accentuation of pulmonary markings. T.C.D., 11 cm. Apex beat 5th. i.s. Pulse, 86; irregular in volume and rhythm. Irregularity present for at least four years. Basal metabolic rate, −4; weight, 184.

Cardiogram: Heart-block, left ventricular preponderance, auricular fibrillation.

Operation: Janurary 15, under local anesthetic, left enucleation resection of large, partially cystic adenoma, showing areas of calcification. Uneventful recovery.

Patient returned to his parish duties completely relieved of symptoms, including subjective sensation of cardiac irregularity. He died from carcinoma of the prostate in October, 1925, two years and nine months after thyroidectomy.

In the Montreal General Hospital Clinic roentgen-rays of the neck and thorax are part of the routine examination. In all patients with compression of the trachea we have observed widespread chronic changes in the bronchial tree. Our attention was first drawn to this by Dr. W. A. Wilkins, sometime radiologist to the hospital.

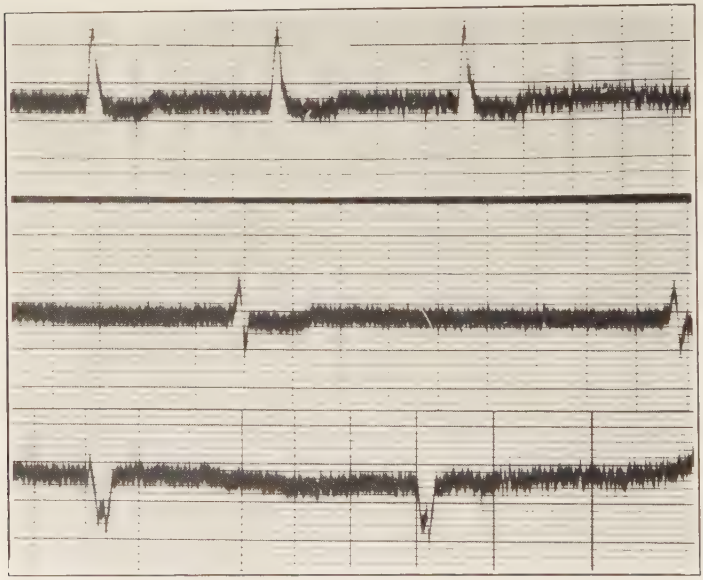

FIG. 43.—Case report No. 25. Heart-block. Left preponderance. Auricular fibrillation.

Because of the obliquity of the upper aperture of the thorax, many of the roentgen-ray diagnoses of intrathoracic growths are fallacious. In true intrathoracic goiters there is dulness on percussion below the level of the clavicle and behind the manubrium sterni. In drawing conclusions from a roentgen-ray, one should visualize the growth not in the oblique plane of the upper opening of the thorax, but in

relation to a plane parallel to the upper border of the manubrium.

Dysphagia due to esophageal compression is a very infrequent complaint in adenomatous disease. In no instance in our series has esophageal narrowing been sufficient to interfere with the passage of the normal food bolus. Difficulty in swallowing occurs in those cases in which bilateral adenomata extend behind the trachea; also in those cases in which nodules, partly detached from the main tumor, are deeply embedded behind the upper pole. These latter nodules, because of their semi-detachment from the body of the lobe, are sometimes overlooked at operation.

Hemorrhage is the most frequent cause of a sudden increase in the size of an adenomatous goiter. This added tumefaction in small growths is accompanied by pain and tenderness, simulating thyroiditis. The frequency with which evidence of hemorrhage within an adenomatous growth is encountered at operation is very striking. The lesion is seen in all stages, comparatively recent blood clot, laminated fibrinous residue, and cyst formation. In cases where the tumor is large and the tracheal airway has been narrowed by compression or by displacement, hemorrhage may produce sudden embarrassment of respiration, or even complete tracheal obstruction. I have on two occasions received telephone calls from physicians in outlying districts for aid in such an emergency. Before anything could be done, however, death had ensued. The general practitioner in rural districts should be capable of applying relief, and for this reason we give an outline of the practical measures which should be tried and which, in a certain number of cases, at all events, will be effective.

A large hemorrhage into an adenoma causes compression of the bloodvessels, especially the venous channels, and leads to edema, and the edema leads to a gradual increase in the size of the tumor. A considerable part of this edematous fluid finds its way into the zone where the bleeding has occurred, and the involution of the blood clot adds further

to the amount of fluid in this zone. Where grave respiratory symptoms develop some days after the occurrence of the hemorrhage, aspiration of the fluid portion of the swelling gives immediate relief. In fact one might say that, in a certain number of these cases, aspiration is a life-saving measure. If, on the other hand, serious respiratory embarrassment follows shortly upon the occurrence of the hemorrhage, free incision should be practised, the blood clot evacuated, and hemorrhage controlled with a packing of gauze soaked in adrenalin. If these cases can be temporarily relieved by the general practitioner, resection of the growth can be performed later and at leisure. In a small number of cases strangulation occurs before medical aid of any kind can be summoned. It is only now being recognized that hemorrhage into an adenomatous goiter is not an uncommon cause of sudden death.

Hospital practice in the conduct of these cases is illustrated by the following case report:

Case Report No. 26.

Male, aged fifty-four years. Farmer. Admitted February 5, 1924, by ambulance, complaining of enlargement of the neck and difficulty in breathing.

Present Illness: Enlargement of neck present for eight years, with gradual increase in size until two weeks prior to admission, when following a severe spell of coughing there was a sudden increase in size. Dysphagia and stridor developed one week later.

Examination on Admission, 1 p.m.: Very marked enlargement of neck, more pronounced on left side. Tumor elastic. Respiration, 28. Distinct stridor, but no cyanosis. Pulse, 128. Fatigued from train journey. Given morphine $\frac{1}{6}$ grain, atropine 1 150 grain, with great relief. Roentgen-ray showed a large shadow in the neck, extending into the thorax behind the sternum, and displacement of the trachea to the right, with compression. At 6 P.M. respirations became labored and noisy; relieved by morphine and atropine. At 8 P.M. patient quiet and color good; it was decided to post-

pone interference until the following day. The resident surgeon was instructed to insert the tracheal tube and aspirate the tumor, should serious symptoms arise. At midnight there was increased difficulty in breathing and slight cyanosis. The patient was unable to swallow without coughing and choking. Morphine and atropine repeated, without effect. At 3 A.M., February 6, there was marked cyanosis, cold sweat on the face and chest, and restlessness. The respirations were very noisy; the pulse, 160. The patient rapidly lapsed into complete unconsciousness. The tracheal catheter was introduced, with immediate improvement in respirations and color. Oxygen administered. At 3.30 A.M. the catheter became plugged with mucus. Insufflation apparatus attached to the catheter, and air and oxygen given for one hour, with slight improvement in respirations. At 4.30 A.M. a large aspirating needle was introduced in front of the left sterno-cleido-mastoid and 50 cc. of thick chocolate-colored fluid withdrawn. This led to an immediate improvement in the respirations and in about five minutes the patient opened his eyes and answered questions. At 5.30 A.M. the tracheal catheter was removed. Color good. Complete consciousness regained after a lapse of two and a half hours. Subsequently patient slept quietly.

Operation: At 10 A.M. the patient's condition was so greatly improved that it was decided to proceed with the operation under local anesthesia. About 50 cc. of hemorrhagic fluid aspirated from the tumor, with further relief to the breathing. The trachea found to be greatly displaced to the right. The adenoma extended around behind the trachea and down into the thorax to the level of the arch of the aorta. It was incised, and the remains of fluid content, together with a quantity of old blood clot and fibrin, were evacuated. Finally, the capsule of the adenoma was dissected out, leaving behind only the posterior portion of the capsule of the lobe. The whole lobe had been destroyed. The right lobe was normal.

Recovery was uninterrupted. Discharged February 18. Five years later the patient was in perfect health. Gain in weight, 30 pounds. Voice, normal. Pulse, 80. No respiratory symptoms.

In order to forestall fatalities from tracheal compression due to hemorrhage into an adenoma or from laryngeal adductor spasm during or following operation, an intratracheal insufflation apparatus should always be part of the equipment of a surgical goiter clinic.

TREATMENT OF NON-TOXIC ADENOMA.

Adenomatous cases in which toxic symptoms or respiratory embarrassment have developed are usually referred to the surgeon. In the absence of these symptoms, however, the physician frequently feels that operation is not indicated, and prescribes iodine. The advisability of this is a moot point.

In 1928 a survey was made in Michigan "to determine whether iodine in any amount, and especially in amounts used in the prophylaxis of goiter such as iodized salt, could be an etiologic factor in the production of hyperthyroidism." The patients were all adults and many had large adenomatous goiters of long-standing. Patients who had hyperthyroidism before using iodized salt were excluded. The results may be briefly summarized as follows:

Class I.—Of 655 patients who had used iodized salt—88 per cent for four years and 12 per cent for at least one year—27 showed symptoms of hyperthyroidism—4.1 per cent. Pregnancy, infection, and mental shock had, however, supervened in some cases and may have been responsible for the condition.

Class II.—Of 419 patients who had used no iodine, 233 had symptoms of hyperthyroidism—55.5 per cent.

Class III.—Of 114 patients who had used iodized salt and in addition either external applications of iodine or Lugol's solution, there were 20 with hyperthyroidism—17.5 per cent.

Class IV.—Of 41 patients who had taken iodine on prescription but had never used iodized salt, 8 had hyperthyroidism—20 per cent.

When we consider the difference between the percentage of hyperthyroidism in Class I and Class II, between those who had taken iodized salt and those who had taken no iodine—4.1 per cent as compared with 55.5 per cent—we conclude, if a conclusion can be drawn from this number of cases, that minimal doses of iodine (doses sufficient to meet the physiological demands of the gland) tend to prevent rather than to excite hyperthyroidism. With regard to the cases of hyperthyroidism in Classes III and IV, Kimball is of the opinion, after a careful study of these cases, that they were due not to the amount of iodine taken but to the time element alone. Kimball further cites instances of patients with adenomatous goiter who took from 5 to 15 grains of potassium iodide daily for ten years, without developing toxic symptoms. The observations on this latter class, however, are confined to a very small number of cases.

It is the abuse of the drug, however, not its physiological use, which we would strongly deprecate. It is our belief that large doses of iodine may incite hyperactivity in an adenomatous growth and this hyperactivity tends to persist until the goiter is removed or degenerative changes have led to its destruction, by which time irreparable damage may have been wrought upon the cardiovascular system. Indeed, not only may the administration of iodine render quiescent cases toxic, but the toxicosis may be of a very severe type.

It is our opinion that all non-toxic adenomata should be removed, for the following reasons:

1. Because in the ordinary course of events at least 25 per cent will become toxic; at an age, moreover, when the cardiovascular apparatus is especially susceptible to damage.

2. Because the growth will increase in size and in time may cause pressure upon the trachea.

3. Because at any time hemorrhage may occur within the adenoma and cause serious respiratory embarrassment or even sudden death.

4. Because the growth may become malignant.

CHAPTER XII.

DIFFERENTIAL DIAGNOSIS BETWEEN GRAVES' DISEASE AND TOXIC ADENOMA.

While the symptom-complex in toxic adenoma closely resembles that of Graves' disease, there are definite points of differentiation. Broadly speaking, in Graves' disease the brunt of the thyrotoxicosis is borne by the nervous system, while in toxic adenoma it is borne by the cardiovascular system. In adenomatous disease crises do not occur and exophthalmos does not develop; but vascular hypertension is almost invariably present and myocardial changes take place early and are usually permanent.

Graves' Disease.	Toxic Adenoma.
The disease may occur at any age. It most commonly occurs between twenty and forty.	Enlargement of the thyroid makes its appearance usually between the ages of twenty and thirty years.
The symptom-complex, including ocular signs, is fully developed within three months.	The toxic symptoms develop from seven to thirty years after the appearance of the goiter; average, sixteen years.
The symptoms develop so rapidly that the patient is usually incapacitated within from three to six months.	The symptoms are slow in developing, leading to incapacity in from one to three years, the average age of incapacity being forty-seven.
The enlargement of the thyroid, if present, is uniform and smooth, and involves both lobes and the isthmus, over which there is pulsation, a distinct bruit, and not infrequently a thrill.	The goiter varies in size from small discrete single or multiple globular nodules to masses the size of the clenched fist, unilateral or bilateral. The consistence varies from semi-fluctuation to stony hardness. Pulsation and bruit are absent except in rare instances.
Tremor of the hands is marked, increasing in severity. Later tremor may involve the whole body.	Tremor of the hands is definite, but not violent.

Graves' Disease.	Toxic Adenoma.
There is marked nervousness, restlessness, and mental irritability, and sometimes delirium.	Nervousness, restlessness, and irritability are mild in comparison with Graves' disease. There is no delirium.
The appetite is increased.	The appetite is diminished or variable.
Frequently there is vomiting or diarrhea or both.	Vomiting and diarrhea are very unusual.
There is rapid loss of weight and strength. Sweats are common and profuse. Heat intolerance is an outstanding feature.	There is gradual loss of weight and strength. Sweats are infrequent. Heat intolerance is not a marked feature.
Ocular signs usually develop within three months, appearing as widening of the palpebral fissure, lagging of the upper lid, stare, and lack of convergence. In about 90 percent of cases exophthalmos develops within two years.	Ocular signs (widening of the palpebral fissure and lagging of the upper lid) are present only in very exceptional cases and even then are seldom more than suggestive. Exophthalmos is absent.
Wrinkling of the forehead is absent.	Wrinkling of the forehead is present.
The pulse range is from 120 to 140. The systolic blood pressure is usually within normal limits. The pulse pressure is always moderately increased.	The pulse range is from 90 to 120. In long-standing cases it is frequently irregular (auricular fibrillation). There is usually severe nocturnal precordial thumping. The blood pressure, both systolic and diastolic, is increased. Especially marked is the increase in pulse pressure.
There are no pressure symptoms.	In large goiters, especially if unilateral, there may develop, because of pressure upon the trachea or the recurrent laryngeal nerve, huskiness of the voice, frequent hacking cough, and dyspnea upon exertion or when the patient is lying down.
The basal metabolic rate is elevated between +40 and +80. Average, +47 to +53.	The basal metabolic rate varies between +20 and +40. Average, +32.
The action of iodine, in the form of Lugol's solution, is striking, especially in relieving the cerebral symptoms—nervousness, restlessness, irritability, and delirium—and in abolishing the stare.	Iodine may be administered without evident effect. In some cases its effect is rather to increase the nervous symptoms. Only in rare instances is it of definite benefit.

Differential diagnosis is especially difficult in:

1. Cases with diffuse adenomatosis without evident glandular enlargement.

2. Cases in which an active adenoma occupies the lower pole of the left lobe and is not detectable on palpation or visible in the roentgen-ray. In both types, No. 1 and No. 2, the diagnosis of toxic adenoma is based upon the symptom group—tachycardia, tremor, and elevated basal rate, and the absence of eye signs or bruit over the gland.

3. Cases of adenomatous disease in which there are suggestive eye signs but no exophthalmos. These are cases in which the histological feature of adenoid heterotrophy is present, that is, tissue showing the histological lesion of Graves' disease. In such cases a murmur may be audible over the tumor, and iodine is effective in moderating the symptoms and lowering the basal metabolism. These cases probably constitute the majority of those reported as unilateral Graves' disease.

4. Mixed cases, in which Graves' disease and adenoma are combined. It has not been definitely established whether we are here dealing with two separate and independent lesions or whether the adenomatous nodules found in these cases are the result of sclerotic changes in an adenoid goiter. In any event the presence of adenomata is as a rule not recognized clinically, because the nodules are generally small and deeply embedded in the gland. The clinical picture is that of Graves' disease. The patients are usually very toxic. The effect of iodine in mixed cases differs from that produced in uncomplicated Graves' disease. It is thought to stimulate the adenomatous nodules into overactivity, while relieving the dysthyroidism, so that, although it abolishes the more serious nervous symptoms, it may not effect the usual improvement in the pulse rate and basal metabolism. Cases of Graves' disease which react in this way should be suspected of being mixed cases. The resistance of these patients to the usual preoperative iodine

medication means that in the surgical conduct of the case a reversion to the methods of pre-iodine days must be considered, and ligations followed by single lobectomies performed instead of radical excision in one stage.

5. Those chronic cases in elderly people which present the physical signs of adenoma, but in which suggestive eye signs are present and occasionally a murmur over the gland. These are primarily cases of adenoid goiter in which sclerotic changes have led to an irregular lobulation which may closely simulate the adenomatous gland. These cases react favorably to iodine.

CHAPTER XIII.

TOXIC ADENOMA.

In a series of 355 cases of toxic adenoma operated upon in the Montreal General Hospital Clinic from 1921-1927 inclusive, there were 27 males and 328 females.

There was a history of generalized thyroid enlargement during adolescence in 89 cases (25 per cent).

The average age at which the nodule or nodules appeared was 32.1. In 160 cases the disease was unilateral. In 195 cases, bilateral.

The average age at onset of toxic symptoms was 40.1. The immediate predisposing factor could be ascertained from the case history in only a certain number of cases. In these the causes were classified as follows: pregnancy 51 cases (14.3 per cent); influenza, 24 cases (6.7 per cent); physical strain, 20 cases (5.6 per cent); mental shock or worry, 15 cases (4.2 per cent); tonsillitis or bronchitis, 11 cases (3.1 per cent); typhoid, 3 cases (0.8 per cent).

The average basal metabolism on admission was +24. The pulse average on admission was 100. The average systolic pressure was 143; diastolic pressure, 83; pulse pressure, 60. Murmurs were frequent. Cardiograms were taken in 114 cases. Many showed myocardial changes; in 29 there was left ventricular preponderance; in 14 auricular fibrillation; in 12 other abnormalities. All patients complained of weakness, loss of weight, incapacity for sustained effort, nervousness, and rapid pulse. In nearly all cases, contrary to the general rule in Graves' disease, the appetite was diminished. In no instance was diarrhea or vomiting a symptom, although intractable diarrhea was the chief complaint in a case reported by Gordon and Bazin. In many cases nocturnal thumping of the heart was the most distress-

ing symptom. Tremor of the hand, which is generally less marked than in Graves' disease, was present in all cases. Insomnia and headache were occasional complaints. Sweats were infrequent; flushings, common; fugitive erythema, the rule. Exophthalmos was never noted, but in a small percentage of cases there was slight widening of the palpebral fissure and slight lagging of the upper lid. While there was frequently noted a heaving pulsation in the neck, transmitted from the carotids, only rarely was a bruit heard over the growth.

FIG. 44.—Large bilateral adenomatous goiter with hyperthyroidism and marked loss of weight. No eye signs.

These patients frequently have a distraught, hopeless expression and show a total disregard for personal appearance, their bearing and aspect resembling that of the chronic drug addict.

If the adenomata are small, involvement of the thyroid may not be suspected until wasting is advanced. Even then palpation may leave one in doubt as to the presence of

irregularity in the contour of the lobes, but one can, not infrequently, detect an unevenness in the surface of the gland by observing in a strong light its movements beneath the integuments during the act of swallowing. It is especially in cases of diffuse adenomatosis without demonstrable enlargement of the thyroid that medical treatment is likely to be continued in spite of progressive deterioration in the patient's physical condition. Where one meets with the combination

FIG. 45.—The same patient as in Fig. 44, six months after operation. Gain in weight 43 pounds.

of tremor and tachycardia in an individual of middle age, a metabolism test will at once decide whether or not the thyroid gland is responsible for the symptoms.

The only treatment for toxic adenoma is operation. Patients with auricular fibrillation need not be excluded, though there is no type of case in which it is more essential that operation should be delayed until the patient is at the top of his form. There have been in the clinic several such

cases which at the time of admission seemed hopeless from an operative point of view; all, however, with two exceptions, went through radical operations without severe reactions or postoperative complications.

PREOPERATIVE TREATMENT.

Rest in bed amid quiet surroundings almost invariably effects a rapid improvement in the patient's general condition. In cases in which there is auricular fibrillation or dilatation with decompensation, digitalis should be administered.

For two substantial reasons it is our practice to give these patients a course of iodine after admission to hospital:

1. Because in those cases of adenoma with suspicious eye signs it is distinctly beneficial. This is probably due to the presence in the adenoma of the histological features of adenoid heterotrophy (hyperplasia), the tissue resembling that found in Graves' disease.

2. Because in certain cases of adenoid goiter developing in elderly people there is an associated perilobular fibrosis, and in the absence of a bruit or definite ocular signs it is impossible to differentiate the condition from adenomatous disease, especially if only one lobe is palpably involved. Were iodine omitted, these patients would be exposed to serious peril in the postoperative period. We have had several cases of this kind, the preoperative diagnosis being toxic adenoma. One case was admitted *in extremis*, with general anasarca, thrombo-phlebitis of the right brachial vein, and marked cardiac decompensation. A period of two months elapsed before her condition was considered safe for operation. Throughout the latter part of this period iodine was administered in small doses. At operation the gland was found to be of the Graves' type. Convalescence was uneventful. Appended is a summary of the case report.

Case Report No. 27.

Female, aged sixty-one years. Married. Admitted November 26, 1926.

Present Illness: Goiter since age of sixteen; larger past two years. In August, 1926, first noticed swelling of legs, nervousness, tremor, and shortness of breath. At rest, but not confined to bed. For three weeks in October felt better; dropsy disappeared and nervousness was less. Early in November shortness of breath and swelling of legs returned. For past week right arm has been swollen.

Examination: Under-nourished, dyspneic, slightly cyanosed. Occasional cough. Slight tremor of hands. Nervous and irritable. Heat intolerance. Falling of hair. Loss of 20 pounds in weight since October. Suggestion of eye signs, *i. e.*, slight widening of palpebral fissure, slight lagging of upper lid, and pigmentation of lids. Thyroid: bilateral enlargement, moderate grade, more marked in right lobe. Surface of gland irregular: suggestive of adenoma, but no clearly-defined globular mass. Consistence firm. No pulsation, thrill or bruit. Transverse cardiac dulness, 13 cm. Heaving impulse. No murmurs. Pulse 150, irregular in volume and rhythm (fibrillation); marked cardiac decompensation. General anasarca. Marked edema of posterior chest wall; some pleural effusion; abdominal ascites. Right leg much more edematous than left. Marked edema of right arm below junction of middle and upper third of humerus, with firm tender cord in course of brachial vein. Urine, 1.024; albumin, +; epithelial and hyalin casts. Blood urea nitrogen, 28 mg.; creatinine, 1.46 mg.; uric acid, 2.8 mg. per 100 cc. Cardiogram: auricular fibrillation; right ventricular extra systoles.

Treatment: Absolute rest in screened bed. Hand feeding. Digitalis. Restriction of fluids. Salt-free diet. Because of serious condition, not possible to determine basal metabolic rate.

Diagnosis: Toxic adenoma.

December 7, Lugol's solution, 3 ♏ to 5 ♏ t.i.d., begun. January 1, 1927, phlebitis right arm and general edema

completely subsided. Pulse, 88; much less irregular. Cardiac compensation fully reëstablished. Ravenous appetite. January 4, basal metabolic rate, +68; 8th, +63; 13th, +58; 17th, +58.

Operation: January 21, subtotal thyroidectomy under local anesthetic. Operative diagnosis: Graves' disease.

Postoperative Course: At height of reaction, thirty-four hours postoperative, temperature reached 103.4° F., then rapidly subsided. Maximum pulse, 116. Uneventful convalescence.

Pathological Report: Adenoid goiter (Graves' disease).

February 5, 1927. Discharged. Strikingly improved. Heart much less irregular; color good; gaining weight rapidly; not nervous or tremulous.

OPERATIVE TREATMENT.

The immediate preoperative preparation is the same as in Graves' disease.

The operative procedure applicable to adenomatous cases is that commonly described as enucleation resection. By this is meant the removal by dissection of all adenomatous tissue with, in the majority of instances, part of the surrounding normal gland tissue.

Local anesthesia is to be preferred.

In large bilateral tumors it is generally expedient to divide the prethyroid muscles. Where the tumor is single and freely movable, though large, one can generally do an enucleation resection quite easily by splitting the aponeurosis in the midline and retracting the prethyroid and sternomastoid muscles. In the resection as much normal tissue as possible should be spared. Before removing one lobe one should determine the presence or absence of the opposite lobe. Congenital absence of one lobe is infrequent but possible, and in such cases one should take pains to conserve all of the normal tissue in the adenomatous lobe and to interfere as little as possible with the arterial supply. Adenomatous nodules are most

commonly located in the lower poles and mid-zones, and one can generally save sufficient healthy tissue to maintain normal physiological function. As a rule the superior thyroid artery should not be ligated. If the tumor is large and unilateral, hemostasis is most easily secured by ligation of the inferior

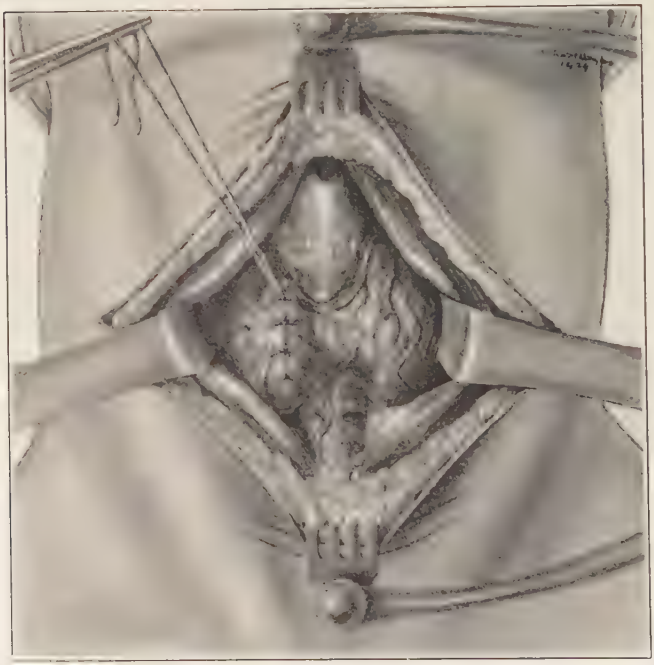

FIG. 46.—Showing method of restoring capsule of remnant of right lobe after resection of adenoma.

thyroid artery. No nodules should be left behind. Failure to extirpate all of the adenomatous tissue in both lobes is responsible for the so-called recurrences in these cases. Frequently on delivery of the left lobe, there is found in the lower pole an adenoma which was not detected on palpation. The mediastinum should also be palpated. The vessels entering

the under surface of the nodules should be separately ligated; the capsular vessels should be tied off, and the lobe restored by approximation of the margins of the defect with interrupted sutures of catgut. (Fig. 46.) In large tumors, where the lower pole is engaged in the upper aperture of the thorax, it is generally easier to perform the resection from above downward, gradually delivering the lower pole. In a considerable number of cases the lower poles extend below the level of the sternoclavicular joints and manubrium sterni; these cases, however, should not be described as intrathoracic.

True intrathoracic growths are in many instances connected only by delicate fibrous bands to the adenomatous masses in the lobes. For this reason, enucleation resections confined to the lobes may fail to relieve the toxicity or such symptoms as upper thoracic pain and tracheal compression. Careful palpation of the mediastinum on the completion of lobe resections is not a wholly reliable means of detecting intrathoracic growths; a preoperative roentgen-ray of the upper thorax should be a routine practice.

To deliver intrathoracic growths, it is now seldom necessary to divide the clavicle or split the sternum. When the lobar portion of the resection has been completed, the intrathoracic mass can generally be enucleated without risk. Here again local anesthesia, in permitting coöperation on the part of the patient, is a factor in converting a difficult maneuver into a comparatively easy one. When the patient coughs, the dome of the pleura rises and forces the intrathoracic mass into view. At this instant the capsule of the growth is caught with a three-prong clamp and retained in the elevated position. Then, the plane of the innermost layer of the fibrous capsule having been defined, the finger is inserted, and by constant upward traction, aided by repeated expulsile coughing on the part of the patient, the mass is gradually freed. The most important technical point in such an enucleation is the determination of the proper line of fascial cleavage. An error in this regard may lead to injury of the subclavian or

innominate veins. Hemorrhage subsequent to the removal of the mass is easily arrested, because the vascular attachments are carried with the extension of the growth from above downward and the bleeding vessels are all found about the periphery of the upper aperture of the cavity.

Because of the irregularity in growth and consequent deformity of the lobes in adenomatous disease the recurrent laryngeal nerves are frequently very much displaced, and therefore more liable to injury in this operation than in the thyroidectomies performed for Graves' disease. For this reason ligation of the inferior thyroid artery, if desirable, should be performed only after clear exposure, which can best be secured as soon as the lobe has been delivered and before bleeding has obscured the field.

The danger of injury to the recurrent laryngeal nerves is further augmented by the fact that in old adenomatous cases the formation of scar tissue on the posterior surface of the lobe is common, and one may mistake this for the true capsule and proceed from without rather than from within the lobe capsule.

Occasionally respiratory stridor develops. This is especially likely to occur in cases where the prethyroid muscles have been retracted rather than divided. Among the cases operated upon at the Montreal General Hospital two instances of this most distressing emergency have occurred. From a careful study of these cases I feel convinced that the respiratory obstruction was due to a temporary spasm of the adductors. These cases have been described as tracheal collapse, but, as Colp and Louria have shown by experimental work, tracheal collapse rarely occurs. One other possible explanation is that the novocain injected infiltrated the recurrent laryngeal nerves, causing abductor paralysis. This theory has been discarded in the cases here recorded because of the short duration of the first attack and because of the lapse of two and a half hours before the onset of the second attack. It is a striking fact that this complication has not

occurred in the cases in which the roentgen-ray has shown definite narrowing of the trachea. Tracheotomy should be performed only if there is not available an intratracheal insufflation apparatus — a contingency which should never arise in a clinic where thyroid work is done.

Case Report No. 28.

Female, aged forty-two years. Admitted March 22, 1926. Pulse, 114. Tremor of hand. Basal metabolic rate, +43. Roentgen-ray showed trachea displaced to the right.

Diagnosis: Toxic adenoma.

Operation: March 26, bilateral enucleation resection, under local anesthetic. Prethyroid muscles retracted. A large adenoma in the left lobe resected without complaint of pain or discomfort. During resection of two small nodules in the right lobe, however, inspiratory stridor and dyspnea developed. It was thought at the moment that the stridor might be due to bilateral compression of the trachea by the retracted prethyroid and sterno-cleido-mastoid muscles. This compression was relieved by the use of retractors, and the trachea, which showed no evidence of collapse or deformity, was supported with forceps on each side. The head was elevated. The tracheal catheter was ready for insertion but the attack passed off, the patient having reached a stage of moderate cyanosis only. Operation then completed and wound sutured. The patient left the table in good condition. A second attack suddenly developed three and a half hours later, in the ward. By the time the tracheal catheter had been introduced, the patient was deeply cyanosed and was rapidly losing consciousness. Relief was immediate. There was no sign of secondary hemorrhage. The catheter was left in position for twelve hours. Laryngoscopic examination at 10 A.M. on the next day showed that the movements of the vocal cords were normal.

Another patient from the clinic, operated upon by Dr. C. K. P. Henry, presented identically the same clinical features,

namely, a primary attack of dyspnea with stridor during operation and a second more serious attack some time after returning to the ward, relieved by intubation. In this instance, too, the innervation of the vocal cords was shown to be normal.

R. P. Ball reports 4 fatal cases of pulmonary atelectasis following thyroidectomy, with injury to the recurrent laryngeal nerve - unilateral in 3 cases and bilateral in 1. In all 4 cases stridor developed during operation. In 3 tracheotomy was performed immediately after operation and in 1 on the fifth day after operation. The deaths occurred fourteen hours, thirty-six hours, sixty hours, and six days after operation. The cases presented the typical physical and roentgen-ray signs and the postmortem appearance of atelectasis.

Air embolism is especially likely to occur in operations upon very large adenomatous growths, where the venous trunks coursing over the surface of the tumor are excessively large and thin-walled, and liable to be incised or ruptured in the process of enucleation. The best protection against this occurrence is the avoidance of haste and the constant retention of a compression gauge immediately above the sternum, where these large veins converge. This accident occurred once in our series. There was but temporary loss of consciousness; the patient died, however, shortly after returning to the ward. Small air emboli may not give rise to symptoms, but in this case (Case Report No. 29) there was very audible churning of the blood within the heart.

Case Report No. 29.

Female, aged seventy-five years.

Admitted: May 16, 1925.

Diagnosis: Non-toxic adenoma.

Present Illness: Goiter present for thirty-five years, gradually increasing in size. Growth more rapid past few months.

Clinical Features: Massive tumor left lobe. Smaller adenoma of right lobe. Trachea displaced to right. No symptoms of hyperthyroidism. Heart not enlarged. Pulse 80, regular. Blood pressure, 140/80.

Operation May 19: Local anesthesia. Division of prethyroid muscles and sterno-cleido-mastoid on left. Cystic adenoma 13 x 10 x 9½ cm. delivered. Considerable bleeding from large thin-walled veins. At this juncture the heart's action became audible, the sound resembling that produced by the rapid and alternate ejection and aspiration of saliva through the teeth. The patient became pale and unconscious. There was but little disturbance of the pulse rate. The swishing sounds lasted about thirty seconds. Given intravenous glucose saline, 700 cc. The left-sided tumor, together with a smaller mass on the right side, rapidly removed and the wound sutured. At completion of operation patient fully conscious and pulse volume restored. Placed in bed in operating room and given within the hour transfusion of 500 cc. universal blood. Returned to ward in good condition.

Postoperative Course: Three hours postoperative developed chill. Later, marked cerebral irritation, attributed to multiple air emboli of cerebral cortex. Pulse, 92.

Death: Five and a half hours postoperative.

Autopsy (except head): Heart, 470 gm., not dilated. Lungs showed congestion of both lower lobes. General arterial sclerosis. Chronic nephritis.

FIG. 47.—Massive adenomatous goiter, the right lobe prominent and overriding the clavicle. At operation the left lobe found to be the larger, to be deeply placed in the neck, and to extend into the thorax.

FIG. 48.—Photograph of gross specimen.

DIFFERENTIAL DIAGNOSIS.

Thyroglossal Remnants.—Cyst formation or hypertrophy in a thyroglossal remnant situated in the mid-line or immediately to the left of it, especially if at the site of the pyramidal lobe, is not infrequently mistaken for an adenomatous tumor. Occasionally these tumors contain actively secreting thyroid tissue. The basal metabolism should be determined, and, before the tumor is removed or its vascular supply interfered with in any way, one should make sure that thyroid tissue is present in the normal location.

Extra Cervical Rib.—Two cases were observed in the Montreal General Hospital Clinic in association with adenomatous goiter. In one case the goiter was thought by the patient to be responsible for pain and tingling in the left hand. In the other, it was thought to have been the cause of "a stroke" which had occurred five years previously and had resulted in partial loss of power and muscular wasting in the right arm. Where pain referred down the arm, especially the left, is associated with benign toxic goiter, the possibility of an extra cervical rib being the cause should be excluded by roentgen-ray.

In a total number of 1050 thyroid cases treated surgically, anginal pain referred to the left wrist was noted in only one patient, a woman, aged fifty-nine years, with toxic adenoma. The pain ceased after operation and has not recurred. It is now seven and a half years since operation.

CLINICAL TABLES.

		Per cent.
Total number of cases	355	
Males	27	7.6
Females	328	92.4
Age on admission, average	42.6	
Youngest	15.0	
Oldest	71.0	
Married	253	71.0
Single	102	29.0
Occupation:		
Housewives	204	
Office clerks and typists	20	

Clinical Tables—*Continued.*

Occupation:		
Domestics	12	Per cent.
School teachers	10	
Trained nurses	9	
School girls	2	
Not recorded	98	
History of goiter among immediate relatives in	120	33.8
Goiter in adolescence in	89	25.0
Immediate predisposing factors:		
Pregnancy	51	14.3
Influenza	24	6.7
Physical strain	20	5.6
Mental shock or worry	15	4.2
Tonsillitis or bronchitis	11	3.1
Typhoid	3	0.8
Age at appearance of adenoma, average	32.1	
Age at appearance of symptoms, average	40.1	
Unilateral enlargement in	160	45.0
Bilateral enlargement in	195	55.0
Displacement of trachea in	164	46.2
Roentgen-ray of upper thorax in	152	
Substernal goiter in	26	17.1
Compression of trachea in	26	17.1
Pulse rate on admission, average	99.7	
Pulse irregular in	27.0	7.6
Pulse regular in	328.0	92.4
Electrocardiograph taken in	114	
Auricular fibrillation in	14	
Left preponderance	29	
Extra systoles	6	
Other abnormalities	6	
Normal tracing	59	
Systolic blood pressure, average	142.6	
Diastolic blood pressure, average	83.1	
Pulse pressure, average	59.5	
Basal metabolic rate:		
First untreated basal metabolic rate, average	+23.8	
Immediately before operation, average	+19.8	
Postoperative, average	+ 6.5	
Operation:		
Unilateral enucleation resection		160
Bilateral enucleation resection		195
Anesthesia:		
Local		341
General		6
Combined, local and general		8
Postoperative complications:		
Wound infection (mild)		7
Secondary hemorrhage		2
Temporary auricular fibrillation		6
Unilateral recurrent laryngeal nerve injury		2
Temporary mental derangement		2
Results:		Per cent.
Deaths	3	0.8
Working, but with mild residual hyperthyroidism	4	1.1
Cured	348	98.0

Case Reports of Patients who Died Following Operation for Toxic Adenomatous Disease.

Case Report No. 30.

Male, aged sixty years.

Admitted: May 25, 1923.

Diagnosis: Toxic adenoma.

Present Illness: Large adenoma, left lobe, present for fifteen years. A sudden increase in size three years ago coincided with development of toxic symptoms. Following an attack of influenza in January, 1923, patient was confined to bed for three months. For six weeks of this period he had edema of both upper and lower extremities.

Condition on Admission: Pale. Edema of ankles. T.C.D., 14 cm. Pulse, 96 to 108; irregular in volume and rhythm. No eye signs.

Cardiogram: Auricular fibrillation. Left ventricular preponderance. Right ventricular extra systoles.

Basal Metabolic Rate: May 25, +54; June 2, +44.

Treatment: Given course of digitalis. (No iodine.) Pulse range for forty-eight hours before operation, 68 to 88.

Operation June 5, 1923: Local anesthetic, novocain with adrenalin. The skin incision had just been made when the patient gave a convulsive movement and cried out. The face became cyanosed, the pupils dilated. Pulse not obtainable.

Death on table—cardiac. (Adrenalin?).

No autopsy.

Case Report No. 31.

Female, aged forty-five years.

Admitted: October 18, 1923, to medical service.

Diagnosis: Toxic adenoma.

Present Illness: Goiter for five years, developing after influenza. Nodular type. Palpitation and nervousness for four and a half years. Edema of legs for one year.

Family History: Father died of angina pectoris. Mother died of heart disease.

Complaints: Swelling of legs and abdomen, palpitation, nervousness, dyspnea.

Clinical Features: Pale. Poorly nourished. Orthopneic. Lungs clear. R.C.D., 5/15 cm. Gross arrhythmia. Soft systolic murmur transmitted to axilla. Pulse, 120; irregular. Blood pressure, 144/70. Marked edema of legs and buttocks. Ascites. Enlarged liver.

Cardiogram: Left preponderance; auricular fibrillation; inversion of *T* in all leads.

Treatment: Decompensation promptly relieved by rest and digitalis. On October 28, R.C.D., 2.5/9 cm. Pulse, 84.

Operation November 5: Bilateral enucleation resection. Local anesthetic; 1 per cent novocain with adrenalin for skin incision, 0.5 per cent novocain for deeper injections. Returned to ward in good condition.

Postoperative Course: Pulse at 6 P.M., 108. During evening developed cardiac dilatation. Died 12.45 A.M. November 6, fifteen hours postoperative.

Autopsy: Myocarditis. Edema of lungs. Cirrhosis of liver (early hob-nailed).

Case Report No. 32.

Male, aged twenty-eight years. Farmer.

Admitted: December 8, 1925.

Present Illness: Goiter appeared at age of fourteen. No increase past twelve years. Weakness, loss of weight, tremor, tachycardia, and vomiting began in August, 1925. Seen by physician in September. Basal metabolic rate, +78. Under rest and Lugol's solution, 5 ♏ b.i.d., vomiting ceased and neck became smaller.

Clinical Features: Pale. Excitable. Anxious expression. Very nervous, restless, and irritable. Loss of 25 pounds since August. Loss of strength. Quadriceps weakness marked. Large, firm, globular, right antero-lateral thyroid tumor. Slight widening of palpebral fissure and lagging of upper lid. T.C.D., 12.5 cm. Systolic murmur over whole precordium. Pulse, 112. Blood pressure, 150/70. Cardiogram, normal. No focus of infection.

Clinical Diagnosis: Either mixed type or adenoma undergoing adenoid heterotrophy.

Treatment: Rest; isolation; Lugol's solution, 10 ♏ to 15 ♏ t.i.d.

Basal Metabolic Rate: December 10, +83; pulse, 94. December 17, +77; pulse, 110. December 29, +83; pulse, 108. January 4, +83; pulse, 106. January 13, +70; pulse, 108. January 18, +77; pulse, 96.

Operation January 20, 1926: Open ether anesthesia. Enucleation resection of large encapsulated adenoma, right lobe. Left lobe not enlarged. Pulse at end of operation, 130.

Postoperative Course: After midnight became restless and irrational. Temperature rose to 104.4° F.; pulse, 150

Death: 1 P.M. January 21, twenty-seven hours postoperative.

Cause of Death: Congestion of lungs; right-sided cardiac dilatation; postoperative thyroid crisis.

Pathological Report: Adenoma showing thick fibrous connective-tissue capsule. Peripheral zone, compact cellular tissue composed of small acini with practically no lumina; very little colloid; high columnar epithelium. Beneath outer compact zone sections show an intermingling of large acini lined with high columnar epithelium and showing very marked budding. Increased vascularity, but no increase of lymphoid tissue. No invasion of capsule or of bloodvessels.

Diagnosis: Benign adult adenoma, rapidly growing and showing adenoid heterotrophy (the tissue of Graves' disease).

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CHAPTER XIV.

INFLAMMATIONS OF THE THYROID GLAND.

Inflammation may develop in either a normal or a goitrous gland. If in a normal gland, it is called thyroiditis; if in a goitrous gland, strumitis. It may be simple, suppurative, or specific, and may give rise to an impairment or suppression of function which is sometimes permanent. Generally speaking, it is the effect of the lesion rather than the lesion itself which lends importance to this group of cases.

A differentiation between thyroiditis and strumitis may in certain cases depend not upon the palpable features of the gland but upon the history, whether or not there was previous enlargement.

Failure of function may occur (as in Case No. 39) without history of infection or clinical evidence of inflammation (pain and tenderness), the diagnosis of strumitis being sustained only by the palpable change in the size and consistence of the gland.

Of the pathology of simple thyroiditis and strumitis we know very little, because of the paucity of pathological material. Only cases of strumitis in an adenomatous gland are suitable for operation, and these cases are more often suppurative than simple or toxic. Where myxedema follows in the wake of such inflammations, we can at best but postulate the various stages in the degenerative process. The material from Case No. 35, here reported, in which thyroidectomy was performed after a clinical diagnosis of Graves' disease, has, however, afforded an opportunity for a more detailed histological study and a comparison of the sequelæ in cases of this type operated upon and those not operated upon.

Because of awakening interest in the toxic forms of thyroid

inflammation, including ligneous thyroiditis, the following classification is destined to undergo readjustment, the ultimate classification awaiting the definite establishment of the etiology of these lesions.

CLASSIFICATION.

I. *Thyroiditis*: (*a*) Simple (toxic)
(*b*) Ligneous
(*c*) Suppurative
(*d*) Specific
(1) Syphilitic
(2) Actinomycotic
(3) Tuberculous
(*a*) Miliary
(*b*) Caseo-suppurative
(*c*) Lardaceous
(4) Parasitic (Chagas' disease)

II. *Strumitis*: (*a*) Simple (toxic)
(*b*) Suppurative
(*c*) Specific

THYROIDITIS.

Primary simple (toxic) thyroiditis occurs without demonstrable cause. It is usually accompanied by pain and tenderness, rarely by fever. In the nodular form the process involves one part of the gland after another. It may terminate in complete resolution or in partial impairment of or complete suppression of function. Patients who develop this lesion may give a history of remote infection influenza, tonsillitis, furunculosis. Primary simple thyroiditis is said by Osler to have occurred in epidemic form.

CASE REPORT NO. 33.

Male, aged fifty-four years, commercial traveller. Seen November 1, 1926, complaining of a tender swelling in neck, night-sweats, and loss of appetite.

Present Illness: Early in October, 1926, noticed enlargement of neck, with right-sided cervical pain. Weakness, with pallor and night-sweats, developed a few days later. General physical examination by Dr. Lafleur negative.

Examination. Hard nodular enlargement of isthmus and both lobes, the right being the larger. Marked tenderness over right lobe, though ten days earlier tenderness had been chiefly in left. Free movement of gland on deglutition. No tremor. Eye signs absent. Weight, 119. Temperature, 99° F. Pulse, 88 Blood pressure, 122 76. Teeth and tonsils, normal. Basal metabolic rate, +12.

Diagnosis: Primary simple thyroiditis.

Treatment: Rest in bed and application of evaporating lead lotion.

On November 11 right lobe no longer tender; slightly smaller; very hard. Night-sweats still present. On November 26 right lobe still smaller. On December 16 basal metabolic rate, −1; weight, 130; good appetite; thyroid normal in size and consistence. On March 17, 1927, basal metabolic rate, −5; weight, 124½; pulse, 84; patient working steadily and feeling better than for several months.

Secondary simple thyroiditis (toxic) is due to a recent or contemporary general infection such as influenza, pneumonia, puerperal fever, scarlet fever, erysipelas, typhoid fever, rheumatism, malaria, measles, or mumps, or to a recent or contemporary local infection such as cellulitis, tonsillitis, or furunculosis. If due to mumps, rheumatism, malaria, or measles, suppuration does not occur, and the symptoms and outcome are the same as in the primary type. If due to pneumonia, puerperal fever, scarlet fever, or typhoid fever, however, suppuration almost invariably follows, and the condition then passes into the suppurative class.

Even though resolution may seem to have occurred, there is always the possibility of a collection of pus being encapsulated in the center of a lobe, as de Quervain's postmortem studies have shown.

The following case report is illustrative of secondary simple thyroiditis:

Case Report No. 34.

Male, aged forty-two years. Seen November 18, 1925. Complaints: stiffness of neck with swelling and tenderness.

Past History: Measles, scarlet fever, diphtheria, typhoid fever, pneumonia. Numerous severe septic infections of hand, forearm and leg during past nine years, each lasting several weeks.

Present Illness: Six weeks ago stiffness developed both sides of neck. One week later swelling and tenderness noted.

Examination: Thyroid enlarged, hard, tender. No symptoms of hyperthyroidism. Diagnosis: thyroiditis, a potential case of myxedema.

Nov. 25, 1925	BMR − 1		
Jan. 13, 1926	BMR −14	No thyroid tenderness.	
Jan. 29, 1926	BMR −14	Eyes puffy in morning. No energy.	
Feb. 3, 1926	BMR −27	Slight puffiness about eyes. Sleeps 12 to 14 hrs.	
Feb. 10, 1926	BMR −25	.....	Thyroid extract (whole gland), 2 gr., b.i.d.
Feb. 17, 1926	BMR −30	.....	Thyroid extract 4 gr., b.i.d.
Feb. 24, 1926	BMR −32	Tired. Numbness of hands and feet. Skin dry. Memory poor. Hair falling out.	Thyroid extract 4 gr., t.i.d.
Mar. 3, 1926	BMR −17	Symptoms of myxedema receding.	
Mar. 10, 1926	BMR −17	.....	Thyroid extract 5 gr., t.i.d.
Mar. 17, 1926	BMR + 4		
Mar. 31, 1926	BMR − 4	More energetic. Working 6 to 8 hrs. a day.	
April 7, 1926	BMR − 1	.....	Thyroid extract 5 gr., t.i.d.
April 21, 1926	BMR + 3	.....	" " "
May 5, 1926	BMR − 7	.....	" " "
May 19, 1926	BMR + 4	.....	" " "
June 30, 1926	BMR − 1	Weight maintained at 145.	" " "
July 28, 1926	BMR − 8	.....	" " "
Aug. 18, 1926	BMR − 9	.....	" " "
Jan. 26, 1927	BMR − 6	.....	" " "
Mar. 16, 1927	BMR + 4	.....	" " "

Four cases were observed in the clinic which in the early stages presented the clinical syndrome of mild Graves' disease, with tremor, tachycardia, increased heat production (from 30 to 50 per cent), and the added features of pain and tenderness. There were suggestive eye signs in 3 of the cases. Two of these cases were operated upon, and 2 not operated upon. The ultimate result in all 4 cases has been similar, that is the development of a definite and persistent hypothyroidism. It has been found in other clinics that at least one-third of these cases develop myxedema; and that in the remaining cases either there is a mild though persistent insufficiency, the basal metabolism ranging between −10 and −15 per cent, with susceptibility to cold and impaired energy, or else sufficient parenchyma survives to meet normal physiological requirements.

Operation of course should not be performed if the condition is recognized. It is a safe rule to defer operation upon patients presenting the Graves' syndrome if pain and tenderness are added symptoms.

The following clinical report from this group illustrates the symptomatology and course of the disease:

Case Report No. 35.

Female, aged twenty-seven years, school teacher. Unmarried. Seen May 31, 1923, complaining of enlargement of the neck, shortness of breath on exertion, palpitation, constant fatigue, excessive appetite, nervousness, and tremor of the hand.

Past History: Diphtheria, measles, whooping cough, chickenpox, scarlet fever, in childhood. In 1918 she had a number of boils.

Present Illness: Enlargement of the thyroid first noticed in July, 1922.

Examination: Skin moist. Tremor of hand. Nervousness. Heat intolerance. Eye signs—widening of palpebral

fissure and lagging of upper lid. Thyroid uniformly enlarged. Loud bruit over right lobe; none over left. Whole gland tender. Pulse, 108. Blood pressure, 110/20. Weight, 101 pounds. Preoperative basal metabolic rates, at intervals of five days, +51, +44, +38.

Clinical Diagnosis: Graves' disease.

Operation: June 19, under local anesthesia, subtotal thyroidectomy, leaving behind a mass of tissue on each side equivalent in volume to about one-third of a normal lobe.

Histological Report: The tissue is made up of small vesicles lined with high epithelium. There is a definite diminution in the amount of colloid. The most striking feature is the number of lymphoid cells of which there are large aggregations. Some of these groups of cells have definite germinal centers. In other areas the lymph cells are spread in a diffuse way among the vesicles. Diagnosis—thyroiditis.

In September, 1923, the patient complained of swelling of the face and neck and lack of energy. The basal metabolism was found to be −26. Thyroid extract (whole gland) prescribed, 1 grain t.i.d. On November 16 basal metabolic rate, −6; pulse, 106. Thyroid extract reduced to 1 grain, u.i.d. On December 15 basal metabolic rate, −22; weight, 96½ pounds; pulse, 76. Thyroid extract increased.

On June 11, 1927, basal metabolic rate, +6; weight, 87 pounds. Since February, 1924, she had been taking thyroid extract in varying doses, the basal metabolic rate ranging between −20 and +17. During the previous winter had taken 10 grains daily.

Seen again June 25, 1928. Weight, 110 pounds. Taking thyroid extract, 10 grains, daily. Feeling energetic. Pulse, 72; regular. Sleeping well. Heart normal. Blood pressure, 118/70. After an interval of two years menstruation had been reëstablished in October, 1927. Teaching steadily. Apparently in normal health.

Treatment of Simple (Toxic) Thyroiditis.—During the acute stage the patient should be kept at rest in order to reduce to a minimum the demands upon the thyroid gland. A simple

diet should be prescribed. An ice-collar or the application of evaporating lead lotion relieves the feeling of tension, the tenderness, and the pain.

In the treatment of the hypothyroidism resulting from thyroiditis, thyroid gland preparations are of course indicated. It has been found that preparations of the whole gland permit of a more accurate gradation of dosage. The output of a damaged thyroid gland may vary greatly for a year or even longer, and, in order to adjust the dosage accurately to body requirements, metabolic tests should be made frequently. Without this control one is apt, especially at the commencement of thyroid gland therapy, to prescribe too large doses. In time the patient comes to know exactly what dosage corresponds to a feeling of well-being. When this knowledge has been acquired, basal tests are no longer essential, except for the purpose of record.

Iodine in small doses, administered in addition to thyroid extract, is of distinct value in these cases.

During the period of glandular readjustment, even though the basal metabolic rate may be maintained at a normal level by thyroid gland derivatives, patients complain of lack of vigor, susceptibility to cold, and impairment of appetite. The weight is below normal. Menstruation is frequently suppressed. The pallor is striking, though the blood count may be normal. Eventually, however, a state of equilibrium is attained, and on a fixed daily dosage of thyroid extract the basal rate ceases to fluctuate. The appetite improves; normal vigor is restored; there is a substantial gain in weight; menstruation is reëstablished; and the patient resumes work without evident impairment of mental or physical capacity.

Ligneous Thyroiditis.—Ligneous thyroiditis, described by Riedel as "eisenharte strumitis," by Delore and Alamartine as "thyroidite ligneuse," and by Ewing as "benign granuloma," is the most interesting of the thyroid inflammations.

It consists of a stony-hard, smooth or finely-nodular tumefaction. It is at first limited to part of one lobe, but later becomes diffuse, spreading with increasing rapidity throughout the whole gland and laterally into the carotid sheaths. There is but moderate enlargement. Pain is usually absent, but may be a marked feature, as in the case here reported. There is early fixation to the surrounding structures—the trachea and the carotid sheaths, but rarely fixation to the skin. As the disease progresses suffocative attacks, alteration in the voice, and sometimes dysphagia develop. The general health remains good, although there is impairment of energy. The temperature is normal. In the early stages the basal metabolism may be moderately elevated; later it falls to normal or slightly below normal. The cervical lymph glands are not enlarged. Wassermann tests have been negative in all cases except one reported by G. and R. Monod.

The etiology is unknown. Tuberculosis and syphilis have been suspected, but no tubercle bacilli or spirochetes have ever been found. Animal inoculations have been negative. Shaw and Smith found atrophy of the adrenals in one case.

Instances of spontaneous resolution have been reported. In other cases the condition has remained stationary for long periods. As a rule, however, the course is progressive.

A differential diagnosis must be made from lues and cancer.

Treatment.—In the treatment of ligneous thyroiditis drugs and roentgen-rays are of no value. Resection of even small segments of the gland has been followed by resolution. Division or removal of the isthmus relieves the tracheal compression and promotes resolution. Widespread extraglandular infiltration, especially of the carotid sheaths, may make operation upon the lobes difficult and dangerous: fatal accidents have occurred from injury to the carotid artery. Tracheotomy should be resorted to only in emergency.

Case Report No. 36.

Male, aged forty-five years. Clergyman. Admitted March 18, 1926, complaining of respiratory distress, enlargement of the neck, and pain referred to the right shoulder and right ear.

Past History: No childhood diseases. Influenza at thirty-seven.

Present Illness: In December, 1924, consulted a surgeon because of nervousness, restlessness, and inability to carry on work. A nodule was found in the thyroid; basal metabolic rate, +31. Operation advised, but refused. Took six weeks rest, without much benefit. In November, 1925, noticed pain referred to the right shoulder and right ear, with some huskiness of the voice.

Condition on Admission: Tremor of hands. Nervousness. Restlessness. No loss of weight. Eye signs—widening of the palpebral fissure, slight pigmentation of eyelids, very slight if any lagging of upper lid. Pulse, 75. Blood pressure, 130/80. No precordial murmurs. Thyroid: ovoid enlargement of right lobe (7 x 4 cm.), thickening of the isthmus, and a small nodule in the anterior margin of the left lobe. Involved portions of the gland stony hard, with smooth surface. The thyroid moved on deglutition. No bruit over the gland. Basal metabolic rate, +1. Weight, 140½ pounds.

Clinical Diagnosis: Carcinoma.

Operation: March 19, under local anesthesia; complete right lobectomy, partial left lobectomy, and removal of isthmus. No gland tissue of normal consistence felt in the right lobe or isthmus. There was a suggestion of infiltration of the prethyroid muscles. Two nodules dissected out of left lobe, the tissue resembling that of the right lobe and isthmus.

Pathological Report: Chronic inflammation, with marked fibrosis. Ligneous thyroiditis.

On April 29 basal metabolic rate, −14. Given thyroid extract, 2 grains daily (whole gland).

Seen again October 25, 1926. During May he had taken 50 1-grain tablets of thyroid; none since. Pulse, 60; weight,

143; basal metabolic rate, −3. The left lobe had diminished in size. The patient said that he did not feel the cold, but he had been unable to resume his work owing to lack of energy.

March, 1929: Patient reported that he was in good health.

Suppurative Thyroiditis. —Suppurative thyroiditis is a rare affection. It occurs most frequently in association with or following pneumonia, puerperal fever, scarlet fever, and typhoid fever, but it may occur in association with influenza, smallpox, or erysipelas, or as a sequence of sinusitis, gingivitis, tonsillitis, or furunculosis.

It is characterized in the early stages by a general swelling of the thyroid gland and infiltration of the surrounding structures, and later by fluctuation. The fever is of the septic type.

Suppuration may be present from the onset of the thyroiditis or it may develop in an apparently simple thyroiditis of several days' duration, even after evidence of resolution.

Treatment consists of incision and drainage. The use of typhoid vaccine has been recommended in thyroid suppuration due to the Bacillus typhosus.

The following clinical record illustrates a case of pneumococcic thyroiditis:

Case Report No. 37.

Male, aged fifty years. Admitted to the surgical service April 15, 1925, complaining of weakness and a painful swelling in the front of the neck.

Past History: Pneumonia four weeks previously.

Present Illness: Five days before admission noticed a swelling over the trachea and some difficulty in swallowing. The swelling increased in size and became painful.

Examination: Pulse, 100. Temperature, 98.4° F. Patient emaciated and extremely weak. Lungs, negative. Heart, normal. Local condition; a soft, fluctuating swelling over

the thyroid, which moved on deglutition. Voice hoarse and feeble. General condition critical.

Diagnosis: Suppurative thyroiditis.

Under 1 per cent novocain, drainage of the abscess. About 60 cc. of thick, greenish-yellow pus evacuated.

Bacteriological Report: Gram-positive cocci in pairs—pneumococcus.

On April 21, after having been irrational for three days, patient died. The wound had drained well.

Autopsy: Abscess cavity in left lobe of thyroid gland. Deep cervical cellulitis (suppurative). Bronchopneumonia. Multiple pulmonary abscesses.

Specific Thyroiditis.—Syphilis occurs in the secondary stage as a diffuse enlargement and in the tertiary stage as a nodular, gummatous process. The diagnosis is made upon the history and blood Wassermann reaction. The tertiary lesions must be differentiated from malignant tumor.

Actinomycosis is a rarity. It is marked in the early stages by a board-like induration, with the characteristic discoloration of the skin, and later by sinus formation and the discharge of granules. Potassium iodide in large doses should be given. As many actinomycotic lesions about the neck and face have been cured by radium, its use in similar lesions of the thyroid would appear to be indicated.

The work of Shimodaira suggests that the thyroid possesses a relative immunity to tuberculosis. There are, however, three distinct types of tuberculous lesions of the thyroid:

1. Miliary (terminal).

2. The caseating and suppurating lesions, which may be unilateral, in which case excision of the lobe is indicated; or bilateral, in which case repeated punctures, quartz-lamp therapy, and climatic treatment are advisable.

3. The diffuse, non-suppurating lesions which convert one lobe or the whole gland into a lardaceous mass (Poncet). In these cases operation is not advisable, but radiotherapy should be carried out after histological diagnosis. Resolu-

tion is followed by fibrosis, and, if both lobes have been destroyed, myxedema is inevitable.

A description of Chagas' disease has already been given in Chapter V.

STRUMITIS.

Strumitis, or inflammation in a goitrous gland, may be simple or suppurative. It usually develops during or after general and focal infections, the commonest of which are pneumonia, typhoid fever, puerperal fever, scarlet fever, tonsillitis, and enteritis. On the other hand, there may be no history of precedent focal or general infection: the condition may be coincident with menstruation (Case No. 38) or arise without demonstrable cause (Case No. 39).

In simple strumitis the usual clinical symptoms are pain, swelling, and tenderness. If there is fever, it is usually slight. There may, however, be no local signs of inflammation, as in Case No. 39, the fibrosis going on to myxedema.

These simple inflammations generally resolve with rest and local applications—the ice-bag or evaporating lead lotion. Occasionally the inflammation persists, and resection of the goitrous tissue is necessary for the relief of pain.

Case Report No. 38.

Female, aged thirty-two years. Married. Seen May 7, 1926, complaining of enlargement of the neck, nervousness, and a feeling of fulness in the head.

Past History: Measles, mumps, whooping cough, and tonsillitis in childhood; three attacks of quinsy prior to 1920; appendectomy in 1923; and typhoid in 1925. Married six years. In January, 1926, operated upon for tubal pregnancy. No other pregnancies.

Present Illness: Goiter first noticed at the age of sixteen. There had been a distinct increase in size during the last three menstrual periods. The nervousness and feeling of fulness in the head had been present since the tubal pregnancy in January.

Examination: Slight tremor of the hand. Nervous. No eye signs. Weight, 123½ pounds. Medium grade of generalized enlargement of thyroid gland, which was soft and not tender. Gland freely movable. Pulse, 76. Blood pressure, 78/118. Basal metabolic rate, −1.

Diagnosis: Colloid goiter.

Treatment: Increased hours of rest; Lugol's solution, 1 ♏ u.i.d., in alternate months; a diet to include sea food and green vegetables.

On June 5, 1926, the patient reported that three days earlier, with the onset of menstruation, swelling and tenderness had developed in the left side of the neck, with pain referred to the left ear. Examination revealed a marked increase in the size of the left thyroid lobe, which was acutely tender. The lobe was freely movable. The temperature and pulse were normal. Basal metabolic rate, +1.

Treatment: Rest in bed and applications of evaporating lead lotion.

Diagnosis: Simple strumitis in endemic goiter.

Seen again on October 22, 1926. Much improved in general health. No tenderness in the gland, but she complained of throbbing in the neck when tired and before the menstrual flow. Pulse, 76. Taking Lugol's solution in alternate months, as prescribed.

Subsequent course of case uneventful.

Case Report No. 39.

Female, aged eighteen years. Unmarried. Seen on March 11, 1921, complaining of enlargement of the neck.

Past History: Chickenpox, measles, whooping cough, and typhoid fever in childhood.

Present Illness: Goiter first appeared at thirteen, after typhoid fever. Gradual increase in size.

Examination: Adolescent goiter of medium size; soft consistence; no nodules. No pulsation, thrill, or bruit. No tenderness. No ocular signs. Pulse, 64; basal metabolic rate, +1. Given small doses of sodium iodide and referred to a physician.

June, 1922, circumference of the neck decreased by $2\frac{1}{2}$ cm. Taking thyroid extract at intervals and small doses of sodium iodide. Although warned of the possible ill effect of muscular exertion upon the thyroid gland, the patient entered as a student in the Department of Physical Training at McGill in October, 1922. Her general physical condition at that time was excellent.

October, 1923, status of the gland unchanged; no symptoms. Three months later the patient developed myxedema. There was puffiness of the face and hands, pronounced slowness of speech, a retarded pulse, and susceptibility to cold. The basal metabolic rate was −30. She was placed at rest and given thyroid extract. The myxedema subsided and the basal rate rose to normal.

The patient was seen again in June, 1927. During the previous year she had been taking from 2 to 3 grains of thyroid extract daily. This dosage maintained the basal metabolic rate at a normal level, however, only when combined with Lugol's solution, 1 ♏ u.i.d. The thyroid gland had become much smaller, and firmer in consistence. The general health was good.

Comment: That secretory insufficiency developed in this instance as the result of strain fibrosis and atrophy is a possibility which must be considered.

In suppurative strumitis, which usually develops in an adenomatous mass, the gravity of the case varies with the type of infection, the general condition of the patient, and the position and size of the goiter. It is characterized by acute pain, tenderness, swelling, infiltration of the tissues of the neck, edema of the skin, a septic temperature ranging between 99° and 104° F., and a rapid pulse.

Free incision and drainage under local anesthesia are indicated. The incision should be placed over the most prominent point of the swelling, where fluctuation can generally be felt. After the evacuation of the pus the cavity should be explored with the finger and all of the adenomatous tissue removed, if possible. Special care should be taken to remove calcareous deposits; if left behind,

they delay healing or cause persistent sinuses. The use of a rubber drainage tube may be indicated. Hemorrhage may be controlled by gauze packing.

If rupture occurs into the esophagus before incision and drainage are carried out, a fistula may form. Spread of the infection beyond the confines of the gland leads to cervical or mediastinal cellulitis. A cervical abscess may rupture into the trachea or esophagus. Of all the complications, however, tracheal compression and laryngeal edema are the most serious. A persistent sinus or fistula can be cured only by resection of the lobe.

Suppuration confined to a single adenoma leads to its destruction, without subsequent derangement of function or deficiency of secretion.

In the subacute suppurative form, where suppuration has occurred in an old cyst or is encapsulated in a nodule, it is desirable to enucleate the mass without opening it. Enucleation is rendered easy by the unusual distinctness of the planes of cleavage, due to inflammatory edema.

Case Report No. 40.

Female, aged forty-six years. Married. Admitted to hospital August 30, 1925, complaining of pain and tenderness in the thyroid gland.

Present Illness: Typhoid fever at thirty-one. Enlargement of the thyroid since about that age. Symptoms of headache, nervousness, and palpitation began in 1921. In October, 1924, right superior thyroid artery ligated in a Baltimore hospital, with slight improvement in symptoms. Recently, increased nervousness. On August 22 patient had a chill, followed by headache and a temperature of 101° to 102° F. A second chill occurred on August 23, and a third on August 27, with a rise in temperature to 104° F. From then until the time of admission the temperature ranged between 102° and 104° F., with increasing pain, swelling, and tenderness over the front of the neck.

Examination: Slight inspiratory stridor. A large, globular, fluctuating swelling over the right lobe of the thyroid,

with acute tenderness. Overlying skin reddened and edematous.

Treatment: Aspiration withdrew from 60 to 65 cc. of dark brown, thin fluid, with relief of the respiratory distress.

Diagnosis: Suppurative strumitis.

Operation: August 31. Incision under local anesthesia. The cavity, which was within an adenoma and from 6 to 7 cm. in diameter, was filled with thin, brownish fluid and soft necrotic tissue. It was curetted and packed. Convalescence was uneventful.

Pathological Report: All cultures yielded pure growths of Bacillus typhosus. The Widal reaction was positive.

On May 18, 1926, the basal metabolic rate was found to be −8. The patient stated that she was feeling better than she had felt for ten years. There had been a gain in weight of 10 pounds. The Widal reaction was still positive. No evidence of cholecystitis was found. In the process of suppuration the original adenoma had been completely destroyed.

Recapitulation. — In the earlier days of the Montreal General Hospital Goiter Clinic sufficient stress was not laid upon the symptoms of pain and tenderness. It is to be presumed that in future more precise observations will be recorded upon thyroid cases presenting these clinical features.

A warning should be uttered against the assumption that all cases of thyroid enlargement, exclusive of adolescent goiter, should be operated upon.

The sudden development of pain and tenderness in an adenomatous gland, with rapid enlargement but without fever, is most commonly due to hemorrhage, and from this condition a true strumitis must be differentiated. Aspiration may be practised as an aid in diagnosis.

In cases of generalized thyroid enlargement, with concurrent tachycardia, tremor, elevation of the basal metabolic rate, *pain and tenderness*, and possibly the presence of eye signs, operation should be deferred until fuller observations have been made, especially upon the trend of the metabolism curve. The older literature contains reports of cases of

Graves' disease which have terminated in gland atrophy and myxedema. Many practitioners attest to having seen such cases. It is a moot question whether the majority of these cases were not primarily cases of thyroiditis manifesting in the early stages the Graves' syndrome. Our experience suggests that such is the probability, and this view is supported by the fact that, in a large series of histological examinations upon tissues from undoubted cases of Graves' disease, inflammatory changes were absent and these patients have not developed hypothyroidism after operation. An explanation of the clinical phenomena is to be sought rather in the quality of the gland product under such conditions of inflammation than in the histological appearance of the tissues.

Cases of mild hypothyroidism resulting from simple thyroiditis or simple strumitis are probably more common than is at present supposed. Recurring attacks of inflammation with progressive impairment of function might be forestalled by early diagnosis and the elimination of the focus of toxic absorption.

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CHAPTER XV.

MALIGNANT DISEASE.

Classification.

(*a*) Malignant adenoma: (1) Fetal
(2) Adult
(3) Papillomatous
(*b*) Carcinoma: (1) Simple
(2) Medullary
(3) Scirrhous
(*c*) Epithelioma
(*d*) Endothelioma
(*e*) Sarcoma.

The incidence of malignant disease of the thyroid is not known. In 2120 cases of goiter seen in the Montreal General Hospital Clinic from 1921 to 1928 inclusive there were 20 malignant cases (0.9 per cent). In 18 of these it was thought from the history that the malignancy had developed in a precursory adenomatous lesion; the incidence of malignancy in the 536 adenomatous cases operated upon in our series was therefore about 3 per cent, a percentage which agrees fairly well with that of other clinics.

Age at Onset of Malignancy. – In Wilson's series of 290 cases a majority of the patients were in the fifth decade, and in his series of 103 cases Breitner points out that 75 per cent had passed the age of greatest physiological activity of the thyroid and sex glands. In the Montreal General Hospital series the youngest was fifteen, the oldest seventy-one years. There were 9 in the sixth decade.

Sex. – Most writers agree with Wilson that the sex ratio is about 2 females to 1 male. In Breitner's series there were

62 females and 41 males, an unusually high percentage of males. In our series there were 17 females and 3 males, a ratio of 5.6 to 1. On the other hand, from the fact that the number of women operated upon for nodular goiter compared with the number of men was, in our experience, in the ratio of about 9 to 1, it would appear that malignant disease is relatively somewhat more common in men.

Location.—Klose and Hellwig are supported by other European writers in the statement that malignant change originates more often in the right lobe than in the left.

Heredity.—Here, as in other forms of malignant disease, the hereditary factor would seem to be indeterminable. Breitner mentions four instances in his series of 103 cases, and Wolff tells of the occurrence of malignant thyroid disease in two brothers. There was a family history of other forms of malignant disease in one instance in the Montreal General Hospital series.

Pregnancy.—Walton points out that not only may we expect a parenchymatous enlargement of the gland during or following pregnancy, but simple adenomas often become larger and harder at this time. In his paper, however, Breitner reports a case in which the onset of malignancy seemed to coincide with the onset of pregnancy. Presumably the rate of growth in malignant disease of the thyroid is accelerated by pregnancy, as it is in malignant disease of the breast. It is unlikely that the cases reported as occurring in pregnancy exceed the normal percentage of malignant change in adenomatous goiter, but the rate of growth is probably increased and the prognosis for this reason rendered less favorable.

Infection.—A history of infection is said by Carrel-Bellard, de Quervain, Speese and Brown, and others to have been present in many cases. The infections reported occurred in the thyroid itself and in distant regions. French writers are particularly insistent upon the frequency of naso-pharyngo-tonsillar infections. There was 1 case in our series with a

coincident thyroiditis, and 3 cases with either dental or tonsillar infections.

Trauma.—Trauma as an exciting factor is mentioned fairly constantly by European clinicians, and in one of our cases trauma was followed by the development of a massive growth which proved fatal within five months.

Preëxisting Thyroid Tumor.—In support of the view that in most cases of thyroid malignancy there has been a previous thyroid tumor, the opinions of a decisive number of authorities can be cited—Speese and Brown, Wilson, Plummer, Balfour, Berry, Walton, Graham, Klose and Hellwig, and Bland-Sutton. Balfour goes so far as to state that cancer is practically not known to have developed in a previously healthy gland. Graham states that 90 per cent of cases originate in a preëxisting adenomatous goiter. A definite history of preëxisting goiter was elicited in 12 of the 20 cases in our series, 11 of the nodular type and 1 of the adolescent type. In 6 other cases, although not definite, the history was suggestive of an earlier lesion. In the remaining 2 cases it was thought from the history that a precursory lesion could be excluded: 1 case was sarcoma, the growth being continuous over a period of five months; the other, a rapid growth following directly upon trauma.

There is, however, considerable evidence in favor of the development of carcinoma in the normal gland. Ewing admits its possibility. Hinterstoesser's 17 cases of diffuse infiltration and the well-known peculiarities of the scirrhous group provide a basis for the claim on purely pathological grounds. The clinical studies of Walton, Breitner, and others, include cases of primary cancer. Breitner believes that in 11 of his 103 cases of thyroid malignancy the gland was previously normal. The majority of his cases were males in the fourth decade, with a tumor history of only four months' duration. Fuller data will probably show that primary cancer does occur, but that, in comparison with the number of carcinomas which arise in previously existing lesions, it is rare.

Duration of the Enlargement.—The duration of the enlargement as stated by the patient varied in our group from one month to forty years, the average being six years. In 6 cases it was one year or less. One must allow for a wide margin of error. Undoubtedly in many instances the enlargement becomes evident only with loss of weight, due either to the progress of the disease or (more often) to the development of hyperthyroidism. In other cases the enlargement is not pronounced and attention is not drawn to it until fixation or respiratory distress develops.

Rapid Growth.—Six of the tumors in our series were rapidly-growing. In each case the entire growth period, or the period of accelerated growth in a hitherto slowly-growing or stationary adenoma, was less than one year; yet the resulting tumor was of considerable size. Herbst includes in this class 25 per cent of his cases. Wilson, on the other hand, states that rapidity of growth is not necessarily indicative of the existence of malignancy, nor of its degree. We would repeat that loss of fat tissue in the neck emphasizes growths previously inconspicuous or reveals those hitherto unsuspected.

Walton summarizes the causes of rapid increase in size as follows: (1) proliferation of tissues, (2) hemorrhage, (3) inflammation. It should be remembered that hemorrhage or inflammatory change may occur in malignant as well as in benign tumors.

The term "acute cancer" used by Craver (who quotes Ewing, Moure and Liebault, and Bowman), designates those rare cases in which growth is exceptionally rapid and suffocation threatens within a few weeks of onset. One of our cases has been placed in this class—the case referred to in the paragraph on trauma.

Emaciation.—Unlike other cancerous growths, malignant disease of the thyroid is rarely accompanied by emaciation unless there is hyperthyroidism. In 4 of our cases loss of weight was attributed to increased heat production.

Pain.—Breitner and others have noted painful sensations in the distribution of the cervical sensory nerves. Pain was not a feature in any of our cases.

Involvement of the Recurrent Laryngeal Nerve.—Involvement of the recurrent laryngeal nerve or cervical sympathetic cord may be due to either pressure or tumor invasion. One case in our series showed paralysis of one vocal cord, due to pressure upon the recurrent laryngeal nerve. Walton reminds us that this may result from the pressure of a benign tumor. In one of Schaedel's cases there was partial motor paralysis of one arm.

Tracheal Involvement.—In 9 of our cases the trachea was found upon examination, or demonstrated by the roentgen-ray, to be compressed or deviated from its normal position. In 3 cases it was narrowed from side to side. Instances of tracheal invasion with hemorrhage and pneumonia have been recorded by Bland-Sutton and Müller and Speese.

Interference with Respiration.—Large tumors may be impacted within the upper aperture of the thorax, and may cause displacement, compression, stenosis, or invasion of the trachea or esophagus, with respiratory embarrassment or dysphagia.

Interference with breathing occurred in 6 of our cases. This is said to be the commonest clinical symptom. This embarrassment to respiration must be distinguished from the dyspnea which accompanies exertion in cases of hyperthyroidism or cardiac weakness. In thyroid malignancy the dyspnea is due to compression and fixation of the trachea or to edema and invasion of the larynx.

Huskiness of the Voice.—Huskiness of the voice may be due to chronic congestion of the larynx, paresis of the muscles of phonation, or cancerous invasion or edema of the vocal cords. The onset may be quite sudden and without evident increase in the size of the tumor (Breitner). It was observed in 3 of our cases.

Dysphagia. Wilson believes that in the early stages dysphagia is due to spasm and in the later stages to pressure.

Breitner found dysphagia present without dyspnea or hoarseness. Berry points out the rarity of dysphagia in benign goiter. He observed it most often in those cases in which the malignant process was situated in the posterior part of the gland. Only one patient in the Montreal General Hospital group complained of it.

Fixation.—In 10 of our cases the tumor was fixed to the surrounding structures, and in 4 of the 17 cases operated upon it was fixed to the trachea. The latter sign, Walton insists, is important.

Hemorrhage.—Hemorrhage into the tumor was not noted in our group of cases. It does occur, however, in malignant thyroid disease and may cause a sudden increase in the size of the tumor with respiratory obstruction. The occurrence of hemorrhage is not in itself a proof of malignancy; in simple adenomatous goiter hemorrhage is the commonest cause of sudden enlargement. Fatal hemorrhages into the esophagus and trachea have been described.

Tachycardia and Hypertension.—In 5 of our cases tachycardia and hypertension were noted. In 1 of these, auricular fibrillation with left ventricular preponderance was present.

Elevated Basal Metabolism.—Four of our patients had an elevated basal metabolic rate. Walton, Klose and Hellwig, Wilson, and Plummer, all support the view that hyperthyroidism may be the first sign of malignant change in a benign goiter. There is as yet no agreement about its frequency. Since the practice of determining the basal metabolism of all thyroid cases has become a routine, the percentage of malignant cases with hyperthyroidism has steadily risen. Herbst records 3 per cent, Boothby 25 per cent, and Simpson 50 per cent.

The association of hyperthyroidism and thyroid malignancy is exemplified in the following case report. The physical signs and symptoms were typical of toxic adenoma.

Case Report No. 41.

Male, aged fifty-seven years. Admitted May 12, 1922, complaining of palpitation, weakness, and loss of weight. He gave a history of the removal of "a small gland" from the left submaxillary triangle one year previously.

Present Illness: Emaciation, tremor, rapid irregular pulse, and muscular weakness were the outstanding clinical features. Basal metabolic rate, +47. Weight, 133 pounds. Cardiogram—auricular fibrillation. A movable globular mass, 6 cm. in diameter, occupied the lower pole of the left lobe of the thyroid.

Clinical Diagnosis: Toxic adenoma.

June 1, under local anesthesia, enucleation resection of left lobe.

Pathological Diagnosis: Adenoma.

Following operation the tachycardia subsided and basal metabolism fell to normal. The patient returned to work on September 5 as a hydrant inspector. By November 15 the weight had risen to 190 pounds.

In September, 1924, he began to lose weight. On October 23 basal metabolic rate was found to be +58; on November 6, +78. At this time appearance of enlarged glands on left side of neck first noted. Later they were found on the right side.

December 18, 1924, readmitted, and bilateral dissection of lymph glands of neck carried out under local anesthesia. The left internal jugular vein removed.

Pathological Diagnosis: Adenocarcinoma of thyroid origin. Roentgen-ray treatments were begun. The patient remained well for eight months. He was then admitted with failing circulation and gangrene of the feet.

Died December 5, 1925. No autopsy.

There was in our series only one case with the full Graves' syndrome. The final diagnosis of this case is still in doubt. The fact that, four years after operation, the patient is well and free from signs of recurrence or metastases, makes it probable that the histological picture led to a false conclusion.

Ewing is the authority most often quoted for the statement that the symptoms of Graves' disease may appear during the development of a malignant tumor and that the characteristic hyperplasia of Graves' disease may go on to malignant growth. Herbst, however, did not meet with one case of malignant disease in 5867 cases of exophthalmic goiter.

Metastases.—Metastases may make their appearance before the original tumor has been detected. Walton states that metastases often appear very early and are not necessarily a contraindication to operation. Authorities differ as to the commonest site of metastatic implants and the frequency of their occurrence. In our cases all metastases occurred in the tissues or lymph nodes immediately surrounding the thyroid. Metastases occur perhaps more frequently than one would conclude from the reports. In 14 of Breitner's cases they were detected only at autopsy. Kraus, whose series includes a large percentage of autopsies, reports the finding of metastases in 90 per cent of his cases.

Metastases to bone have been widely studied. The bone-destroying and bone-forming potentialities of the implants are well known. Joll collected a series of 44 cases of bone metastases associated with normal thyroid or benign goiter. Simpson reviewed 77 cases and his studies led him to believe that the benign nature of the primary growth in such cases had not been proven.

From an analysis of 72 cases reported as "benign metastasizing goiter" Delannoy and Dhallium also concluded that few, if any, of the cases had been proved to be benign. Berard and Dunet maintain that, even though not demonstrated, there must have been in these cases a primary lesion in the thyroid gland.

There has recently been admitted to the general surgical clinic at the Montreal General Hospital a case of bone metastasis with extensive bone destruction and fracture occurring several years after removal elsewhere of a thyroid tumor diagnosed microscopically as benign adenoma. A review of

the sections prepared at that time sustains this diagnosis. This case confirms our statement that sections should be prepared from several segments of all tumors if malignant disease is not to be occasionally overlooked.

True metastases must be distinguished from carcinoma in lateral "aberrant" thyroid tissue, instances of which have been reported by Greensfelder and Bettman, Kamsler, and others.

Invasion of large vessels has, of course, always been recognized, and Breitner includes 7 cases in his series.

Recurrences.—Recurrences took place in 6 of our cases. In 2 of these a still earlier operation had been performed elsewhere.

Since in many instances malignant change is not detected by the pathologist in the primary tumor, we now take the view that a nodule developing in the remnant of a lobe upon which a careful enucleation resection has been performed, with negative histological findings, should be considered malignant until proved to be benign.

DIAGNOSIS OF MALIGNANT DISEASE OF THE THYROID GLAND.

Clinical Diagnosis.—There is, of course, no difficulty in diagnosing clinically a tumor which is growing rapidly, is fixed and hob-nailed, and is associated with glandular enlargement. On the other hand, it is impossible to detect early malignant change in an adenomatous nodule. The hardness of malignant tumors has often been commented upon, but in the thyroid most of the small hard nodules are calcified adenomata. Undoubtedly, were examinations less perfunctory, more cases of malignancy would be recognized or suspected before glandular metastases had occurred. In the absence of pregnancy, fever, or local tenderness, an increase in the size of a goitrous gland with limitation of movement should, in patients over forty years of age,

raise suspicions of malignancy. Walton stresses the irregularity of the outline, the increasing firmness, and the development of toxic signs. Klose and Hellwig point out, on the other hand, that a malignant goiter may not be nodular, and Frieland reports a series of thyroid carcinomas without enlargement of the gland.

The clinician may find some solace in deQuervain's statement that "when malignant degeneration exists in a well-encapsulated goiter, clinical diagnosis is out of the question." Balfour's statement, that the majority of cancers develop deep in the gland and not at the surface, also accounts for many failures to recognize the condition clinically. Balfour's observation coincides with our own experience.

Only 8 of the 20 cases in our series were diagnosed clinically. Six of these were advanced, three of them inoperable.

Operative Diagnosis.—Diagnosis at operation was made in 4 of our cases.

Histological Diagnosis.—As stated in the chapter on Pathology, the ordinary histological features of malignant disease, namely, local infiltration, modified cell structure, and karyokinesis, may in certain thyroid tumors be insufficient evidence upon which to base a diagnosis. There is substantial ground for believing that the most constant single indication of malignant disease in the thyroid gland is the invasion by tumor cells of the blood capillaries. Graham followed up clinically and reviewed histologically 134 cases of thyroid tumor which had been diagnosed and treated as malignant. Of this number 43 cases remained free from local recurrence or metastases, and in all of these invasion of the blood capillaries by tumor cells had not been demonstrable. On the other hand, in every case in which recurrence followed operation, the blood capillaries in the original tumor were found to be involved.

Six of our cases were diagnosed upon histological examination of the primary tumor. In 2 other instances malignancy in the primary tumor was overlooked histologically and

discovered only at a second operation. The importance of examining sections from many different parts of a thyroid tumor has already been pointed out. Although errors of omission and commission still occur, the trend of histological diagnosis is decidedly in the direction of greater accuracy.

DIFFERENTIAL DIAGNOSIS OF MALIGNANT DISEASE OF THE THYROID GLAND.

Berry, deQuervain, and Kraus state that the most difficult clinical differentiation is that between thyroid malignancy and chronic diffuse thyroiditis. In chronic diffuse thyroiditis there is a dense, uniformly hard swelling of moderate size, generally unilateral at first but soon involving the whole gland. The gland moves freely on deglutition, but may be somewhat fixed to the trachea. There is tenderness and frequently pain. Myxedema may develop early. In the nodular type of thyroiditis the differentiation at first sight is even more difficult. Here also there are pain and tenderness and gradual involvement of the whole gland, the nodules receding in one lobe as they develop in the other.

Tertiary syphilis may be excluded by the clinical history and the Wassermann test.

Tuberculosis is rare. In the nodular form the tubercles undergo softening and form abscesses. A Montreal General Hospital patient, a woman aged fifty-six years, had an enlarged thyroid, indurated glands in both posterior triangles, and an elevated basal metabolic rate. Malignant disease was suspected. A resected lymph gland proved, however, to be tuberculous, and the thyroid nodules on resection were found to be simple adenomata.

Craver has discussed the subject of parathyroid malignant tumors and their differential diagnosis. He describes them as small, hard, deeply situated, fixed nodules, attached to one lobe of the thyroid. They develop slowly and do not grow

downward toward the clavicle. They are accompanied by dyspnea, hoarseness and dysphagia.

With reference to differential diagnosis between malignant disease of the thyroid and carcinoma of the cervical esophagus, Trotter states that in esophageal cancer there is at first weakening of the voice, then enlargement of the thyroid gland due to infiltration of its posterior surface, and finally esophageal symptoms. A case observed at the Montreal General Hospital in 1923 confirms this sequence. The patient, aged fifty-eight years, was forced to give up his occupation as an announcer and interpreter in a cinema on account of loss of voice. Physical examination revealed a hard enlargement of the thyroid gland and edema of the vocal cords. Barium films of the esophagus were negative. He failed rapidly and died, and at autopsy a small carcinoma was discovered in the esophagus, with metastases in the larynx and in the thyroid. A second case, similar in all respects, was seen in the service of Dr. F. S. Patch.

TREATMENT OF MALIGNANT DISEASE OF THE THYROID GLAND.

If fatalities from malignant thyroid disease are in the future to be substantially reduced, our efforts must be focussed less upon improved treatment of clinically recognizable malignant lesions than upon the prevention and elimination of those preëxistent thyroid lesions in which malignancy so often originates. Juvenile goiter is frequently the forerunner of adenomatous disease, and with but few exceptions malignant disease of the thyroid is engrafted upon an adenoma which has been present on an average for six years. Although the incidence of malignant disease in relation to goitrous population or nodular goiter is not known, we do know that of the nodular goiters operated upon approximately 3 per cent are malignant. Is it too much to hope that the profession will for this reason, as well as for the other reasons

given in the chapter on Adenomatous Disease, adopt the practice of referring to the surgeon all adenomatous cases? The thyroid gland occupies a unique position in that a warning of possible malignant disease is provided by a precursory lesion which is generally evident clinically for years.

A review of the literature warrants the statement that the operative treatment of clinically evident malignant disease of the thyroid offers little more hope of permanent cure than does the operative treatment of clinically evident malignant disease elsewhere. De Quervain states that cure rather than diagnosis should be the surgeon's goal, and this can be attained only if operation is undertaken early and on no more substantial ground than suspicion. By far the greater number of cases reported as permanent cures are those in which malignancy was not even suspected when operation was performed, the clinical diagnosis being simple adenoma. It is in those cases in which the disease is still confined within the capsule of the adenoma and discovered only upon gross section, or more commonly only upon microscopic examination, that one can feel confident of a permanent result.

As exemplifying the advantages of operation before the presence of malignancy is even suspected clinically, the following case report is included.

Case Report No. 42.

Female, aged fifty-three years. Married. History of goiter of seven years' duration. No toxic symptoms.

Clinical Diagnosis: Adenoma of right lobe. On March 25, 1922, under local anesthesia, the whole of the right lobe removed from within the capsule, together with a gland attached to its lower pole.

Histological Diagnosis: Carcinoma of thyroid, with complete replacement of lymph node with thyroid tissue.

No roentgen-ray treatment. The patient is well, seven years after operation.

From this hopeful prospect we must turn to the less hopeful task of considering what treatment is likely to yield the best results in those cases in which a diagnosis of malignant disease is obvious either upon physical examination or upon exposure of the gland.

In the treatment of thyroid malignancy, as in that of other forms of malignant disease, there are those who advocate the use of radium or roentgen-ray alone, those who would rely wholly upon surgical excision, and those who believe that the best results are to be obtained from a combination of the two methods.

Holfelder and Sudeck both state that malignant thyroid neoplasms show greater radio-sensitiveness than do other malignant tumors, and there would seem to be clinical evidence to support this view. Whether this greater radio-sensitiveness applies to cervical glandular metastases as well as to the original tumor has not been definitely determined. It is Breitner's belief that adenocarcinoma is more susceptible to radiation than are the other varieties of thyroid carcinoma. Sarcoma, on the other hand, was found by Schaedel to be particularly resistant to roentgen-rays, but Perthes considers the outlook here to be as favorable as elsewhere. According to Schaedel the primary tumor is more sensitive to radiation than are the metastases arising from it.

Sudeck, Decourcy and others maintain that, where a clinical diagnosis of malignancy has been made, operation should be withheld and radiation alone employed; while Perthes, who has had a very broad experience, recommends radiation as an adjunct to surgical treatment. In this opinion he is supported by Balfour, Holfelder, and many others. Indeed, at the present time the consensus of opinion is that operation followed by radiation is the most rational practice.

The extent of any surgical operation will of course depend upon the presence or absence of glandular metastases or infiltration of the prethyroid muscles. However localized

the disease, the whole of the involved lobe should be removed. Where there are lymph gland metastases, it may be necessary, in addition to performing block dissection of the cervical nodes, to excise the prethyroid muscles, the sterno-cleido-mastoid, and the jugular vein on the diseased side. The artery should be spared if possible, especially in patients over forty years of age. In such a radical procedure the recurrent laryngeal nerve may have to be sacrificed, and, if the infiltration involves the carotid sheath necessitating the removal of the artery and vein, the pneumogastric as well.

Even cases with glandular metastases, especially where radiation is employed after operation, not infrequently survive for four or five years, ultimately to succumb to intrathoracic or more widely disseminated metastases.

In the early cases, those in which the disease is still intracapsular and diagnosed only at operation or by the pathologist, roentgen-ray treatments should be given at intervals over a period of two years.

Local recurrence or cervical glandular metastases developing after operation should be promptly attacked and radiation renewed. Occasionally even in these cases of recurrence cure may ultimately result. Case report No. 43 is given in detail as a hopeful example of this type. This case was especially unfavorable because of the youthfulness of the patient and the failure to recognize histologically the nature of the condition at the time of the first operation.

In the advanced inoperable cases some relief may be hoped for from radiation with roentgen-ray or radium.

Case Report No. 43.

Female, aged fifteen years. Unmarried. Very obese. Admitted January 7, 1923. History of goiter at age of ten, which disappeared on application of iodine, but recently recurred.

On admission there was general enlargement of the gland with a palpable adenoma in the upper pole of the right lobe. No symptoms of hyperthyroidism. Basal metabolic rate, −5.

Clinical Diagnosis: Adenoma non-toxic. Operation January 12, under local anesthesia, bilateral enucleation resection. An adenoma was found in the left lobe as well.

Pathological Diagnosis: Multiple simple adenomata.

Uneventful recovery. On October 22, 1924, patient returned, complaining of a lump in the neck present for three months. On examination there was found a mass 2.5 to 3 cm. in diameter in the right anterior triangle, on a level with the hyoid bone, movable from side to side, but not moving on deglutition. Temperature, 99.2° F. The possibility of a tuberculous cervical adenitis was at first considered. The tonsils were cryptic. There was general pyorrhea. On November 19, 1924, the mass was definitely larger.

On January 6, 1925, under local anesthesia, a number of glands with infiltrated capsules were removed from the right anterior triangle. On section these glands suggested thyroid metastases. This diagnosis was confirmed in microscopic sections. Roentgen-ray treatments begun.

On April 22 there were palpable glands to be made out along both jugular veins, more marked on the right side at the level of the thyroid. The patient was having roentgen-ray treatments.

On December 26, patient readmitted, and on December 31, under intratracheal ether anesthesia, all glands on the right side from the base of the skull to the clavicle, together with the internal jugular vein, were removed; also the remnant of the right lobe and the isthmus. The remnant of the left lobe was explored and a portion removed. The tissue from the right lobe showed microscopically adenocarcinoma. The lymph nodes removed were free from metastases and for this reason dissection of the left side of the neck was postponed. Recovery uneventful. Roentgen-ray treatments have been continued. The patient, six years and two months after the first operation, remains free from signs of recurrence.

PROGNOSIS IN MALIGNANT DISEASE OF THE THYROID GLAND.

Prognosis depends upon the duration and type of the malignant process. From a clinical point of view cases fall into three categories:

1. Advanced inoperable cases, in which radium or roentgen-ray treatment alone is of any avail. It is very difficult to estimate the effect of radiation in these cases. Breitner had 6 patients who lived for more than three years after beginning treatment.

2. Cases in which there are lymph metastases or infiltration of the prethyroid muscles, or both. Here a combination of radical surgical measures and radiation usually postpones the fatal issue and occasionally leads to permanent cure. A postoperative lapse of from five to six years without local recurrence is not, however, long enough to justify a claim of permanent cure. Craver found that in those patients who died the diagnosis was made later in life than in those patients who survived, and also that the tumor was of longer duration.

3. Those early cases in which a diagnosis of malignancy is made only at operation or upon histological examination, cases in which the malignant process is, with few exceptions, confined within the capsule of an adenoma. It is assumed that these are what Kocher describes as the "really early" cases, in which, he states, operation effects a cure in from 80 to 90 per cent of cases.

Of the Montreal General Hospital series 3 were inoperable. In 10 of the cases operated upon there was infiltration of the surrounding structures or lymph node metastases.

From the pathological point of view, which leaves out of account the time element, we find:

1. That the papillomatous type of tumor is the least malignant. According to Herbst there are 33 per cent of five-year cures.

2. That in cases of malignant adenoma there are 17 per cent of five-year cures (Herbst).

3. That in cases of the carcinomatous type only 5 per cent. survive for five years (Herbst).

4. That sarcoma is always rapidly fatal. Of 11 cases reported by Breitner not one survived operation for more than four months. In the 1 case in our series (No. 44), diagnosed clinically as malignant adenoma, the patient died three months after operation.

Of the 20 cases seen in the Montreal General Hospital Clinic 7 were malignant adenomas, three of which were of the papillomatous type and 1 doubtful (Graves'). Ten were carcinomas, and 1 a sarcoma. In 2 of the advanced inoperable cases no histological diagnosis was made.

Eleven of the 20 cases are known to be alive, the postoperative period varying from a year and a half to seven years. All of the fatal cases, including the case of sarcoma, were advanced.

Case Report No. 44.

(*Sarcoma.*)

Female, aged seventy-one years. Admitted March 26, 1928.

Present Illness: Small lump in right side of neck first noticed five months previously. Grew rapidly for three months; then stationary. Loss of weight.

Examination: A very prominent, right antero-lateral tumor of thyroid, 7 cm. in diameter; very hard; not tender; moving on deglutition, but fixed to the trachea. No palpable lymph nodes. No signs of hyperthyroidism. Pulse, 88: regular. Blood pressure, 140/110. Basal metabolic rate, +9.

Clinical Diagnosis: Malignant adenoma of thyroid.

Operation: April 3, resection of right lobe under local anesthetic. Tumor found to infiltrate right margin of esophagus, which was opened at two points in excising areas of involvement; openings sutured and wounds "bipped."

A narrow packing of "bipped" gauze placed along the esophagus and wound closed. Packing removed on the fourth day postoperative. Serous discharge for seventeen days postoperative. Roentgen-ray treatment. Wound completely healed when patient returned to her home in Ottawa, April 25.

Pathological Report: Spindle-cell sarcoma (see microphotograph Chapter V, Fig. 26).

On May 10, 1928, patient developed signs of widespread metastases and by the end of May local recurrence with dysphagia. Died July 14, eight and a half months after appearance of the growth.

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